20 September 2017
EMA/CHMP/853503/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products' (EMEA/CHMP/SWP/28367/07 Rev. 1)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation (*note two parties requested their comments not to be published*).

Stake-holder no.	Name of organisation or individual
1	Robert Jurold, patient safety, child och youth psychiatry, Stockholm, Sweden
3	Prof Sheila M. Bird OBE MA PhD CStat FFPH FRSE, MRC Biostatistics Unit
4	Christian Funck-Brentano MD, PhD, FESC, Professor of Medicine and Pharmacology, University Pierre & Marie Curie - School of Medicine, Department of Pharmacology & Clinical Investigation Center Paris-Est, Hôpitaux Universitaires Pitié-Salpêtrière – Charles Foix
5	Centre for Human Drug Research, the Netherlands
6	LEO Pharma A/S, Hans Hoogland, Ph.D.
7	Meyer Lifschitz
8	NextraResearch S.r.l.
9	Belgian Association for Phase I Units (BAPU)
10	Association for Applied Human Pharmacology (AGAH e.V.), Hamburg, Germany
11	Prahealthsciences (PRSA global science)
12	MSD
13	Medicines Evaluation Board (MEB), the Netherlands

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Stake-holder no.	Name of organisation or individual
14	Goran Westerberg, La Crocina Pharmaceutical Consultants Lp
15	Astellas Pharma Europe B.V.
16	Duke Early Phase Clinical Research Unit, Duke University Medical Center
17	Hammersmith Medicines Research Ltd.
18	EUCROF - Clinical Trials Legislation Working Group
19	International Plasma Fractionation Association (IPFA)
20	IQ Consortium
21	EUCROF - Early Phase Working Group
22	PAREXEL International
23	Galapagos NV
24	Anna Maria Lepore, Bambino Gesù Childrens' Hospital Phase 1 Units, Rome, Italy San Raffaele Hospital Phase 1 Units, Milan, Italy
25	inVentiv Health Clinique inc., Québec (Québec), Canada
26	ACRO (Association of Clinical Research Organizations)
27	Denali Therapeutics
28	Cell and Gene Therapy Catapult
29	QuintilesIMS
30	The British Pharmacological Society, The Faculty of Pharmaceutical Medicine, Endorsed by RCP
31	Swissmedic, Swiss Agency for Therapeutic Products, Hallerstrasse 7, 3000 Bern 9, Switzerland
32	Paul-Ehrlich-Institut, Germany
33	EUFEMED – European Federation for Exploratory Medicines Development
34	Alexion Pharmaceuticals, Inc.
36	REGenableMED consortium
37	Simbec-Orion Group Limited
38	Takeo Saio, Fuji Toranomon, Orthopedic Hospital Chieko Kurihara, National Institute of Radiological Sciences, National Institute for Quantum and Radiological Science and Technology
39	Club Phase 1, Paris, France
40	EFSPI

Stake-holder no.	Name of organisation or individual
41	Edinburgh Clinical Research Facility Phase I / First in Human Study Review Committee (PISRC)
42	Society of Quality Assurance
43	Novartis
44	The Alliance for Biomedical Research in Europe (BioMed Alliance)
45	CR UK & UCL Cancer Trials Centre – at University College London
46	Medicines for Malaria Venture
47	European Federation of Pharmaceutical Industries and Associations, EFPIA European Biopharmaceutical Enterprises, EBE Vaccines Europe, VE Endorsed by EuropaBio
48	REGENERON PHARMACEUTICALS INC.
49	The Royal Statistical Society
50	F. Hoffmann-La Roche Ltd
51	Biotechnology Innovation Organization (BIO), Washington, DC 20024, USA
52	Greenwich Biosciences
53	Pierre FABRE Laboratory
54	Radiopharmacy Committee of the European Association of Nuclear Medicine

1. General comments – overview

Stake-holder no.	General comment (if any)	Outcome (if applicable)
1	I propose that the guidelines state that all raw data should be open for other researchers and the public. That is an important patient safety question.	This is considered outside the scope of the current scientific guide.
3	*Declaration of Interest:* As Royal Statistical Society vice-president and Honorary Officer for External Affairs in 2006, I proposed and served on the Royal Statistical Society's Working Party on Statistical Issues in First-in-Man Studies (chaired by Professor Stephen Senn). The 10 November 2016 draft EMA Guideline is clearly written, welcome and proportionate. Its scope (lines 111-113) is specifically: "to address FIH and early phase CTs with integrated protocols" and to make "recommendations regarding the non-clinical and emerging clinical PK, PD and safety data to support them". The commentary which follows focuses on statistical issues and refers to recommendations made by the Royal Statistical Society's (RSS) Working Party on Statistical Issues in First-in-Man Studies, please see: Royal Statistical Society Working Party (chair: Prof Stephen Senn, member: Bird SM). *Statistical issues in first-in-man studies. Journal of the Royal Statistical Society, Statistics in Society* 2007; 170: 517 – 579. Please see also forthcoming accepted paper in Pharmaceutical Statistics 2017 by Bird SM, Bailey RA, Grieve A, Senn S which is entitled: *Statistical issues in first-in-human studies on BIA 10-2474: neglected comparison of protocol against practice*.	General agreement.
4	The 2007 guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products was revised in the context of the dramatic accident with BIA 10-2474 which occurred in Rennes in January 2016. This revised version is extensive and lists criteria, items and strategies which represent an ideal of drug development but make it more complex, costly and time-consuming than before. It is unfortunate that the raw data of the BIA 10-2474 trial have not been made available for a thorough analysis so that it could be tested that the revised guideline, if in force at the time of the BIA trial submission, would have prevented the accident. And I am uncertain, but cannot prove, that this would have been the case. For example, in the BIA 10-2474 case, it was emphasized that total inhibition of FAAH (the target enzyme) was almost complete at dose much lower than those which later were associated with major toxicity. However FAAH inhibition was measured in peripheral	The revised guideline aims to address as far as possible the important issues that may need consideration during the process of designing a set of studies in a clinical development programme.

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	leucocytes and I was unable to find data showing that this assay reflect inhibition of FAAH in the brain. A pharmacodynamic definition of the maximum dose makes sense in First-in-Human (FIH) studies but is often quite arbitrarily defined. What would one choose, for example, for aspirin? Also the revised guideline states (line 432) that "A trial design using a [maximum tolerated dose] MTD approach is considered to be unethical for healthy volunteers." Fine in principle but determining the MTD is what FIH studies are supposed to assess so, rather than stating that this is not an objective of FIH studies anymore, one could think of another definition of the MTD. This is where the absence of access to the BIA 10-2474 data is frustrating because there were most probably mild adverse events in the cohorts preceding the 5th cohort where toxicity occurred and this possibly could have generated a warning signal to stop increasing doses. Also, it would have been informative to apply the recommendation of § 8.2.6. using the BIA 10-2474 data and one may have seen that the proposed approach may not have prevented the accident: with a half-life of about 10 hrs (from the little we know) a 2 or 3-day split between subjects in a cohort might not have prevented the accident in subjects within the 5th MAD cohort who began experiencing problems after 5 or 7 days of once-a-day treatment. Difficult to say and impossible to prove without having the raw data. The revised guideline does not help addressing the question of the MTD which could be changed to a submaximal tolerated dose using a clear definition based on non-serious adverse events. To my knowledge, other regulatory agencies such as FDA have not published such a demanding guideline. With Europe adopting alone such a demanding guideline, the consequence may be that FIH studies will simply tend to be performed elsewhere. Naturally, no one should argue that safety is the primary issue for all clinical studies and particularly for FIH studies. The question I believe would have been worth addressing, had the BIA 10-2474 data been thoroughly analyzed, is whether the set of requirements included in the revised guideline would have prevented the dramatic accident of Rennes to occur. In summary, the revised guideline seems almost perfect but raises the question of whether its exigencies will really limit adverse events in FIH studies or simply deport such studies to non-European sites. If other major regulatory agencies such as the FDA do not adopt such demanding rules, we may find ourselves isolated. Of course, if this is truly justified by improvement of subjects' safety this is acceptable and needed. My frustration comes from the fact	

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	that FIH studies (in healthy volunteers) have been mostly safe (and the case of Helen Roche with hexamethonium in 2001 or TGN-1412 in 2006 are quite different from BIA 10-2474 in 2016). The BIAL case is something which no one has ever seen: sudden severe toxicity after 84 subjects had received the drug without apparent toxicity or warning sign (so they say – we do not know for sure). Without a thorough analysis of the BIAL data it is impossible to know if the new constraints introduced in the guideline are truly justified or just excellent in principle but quite theoretical.	
5	In general the text is written in non-restrictive language (using terms such as might/may, etcetera), which allows for interpretation. We feel that this guideline should include directive advice in an unambiguous manner, with a specification of the best practice and clear recommendations. It should also be stated what should be recommended when best practice is not possible including a explanation in the protocol. In addition several multi-interpretable words are used in the in the document. We would like to recommend using an internationally applied 'Recommendation Grading System', such as the grading system used by the National Guideline Clearinghouse. This will make the document easier to read (especially for non-native English speakers), and the recommendations less open to interpretation. In line with this, it may also be good to include the level of evidence for all recommendations. Naturally we welcome the fact that PD measures are added in order to facilitate the link with the non-clinical experience and support dose escalation decisions. Finally the text could be structured more clearly. In the current draft version there is a lot of repetition of the same statements in different parts of the document.	General agreement. The final document has been significantly edited to avoid repetition where possible. However a grading system has not been applied as this would not be n line with usual EMA scientific guidance.
5	**4. General considerations** This section should refer to the publication by Kenter MJ, Cohen AF in the Lancet (Establishing risk of human experimentation with drugs: lessons from TGN1412, 2006; 368, pages 1387-91). Structured steps in risk assessments could be provided by CHDR as described in Chapter 11 from CHDR Clinical Study Protocol template.	While the exact proposed structure has not been implemented, the concept of an uncertainty (risk based) approach has been introduced in this section and throughout the guideline.

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5	**4.2 Nature of the target** This is not a full list and needs additional aspects. In addition the sponsor is specified, however it should also be stated that the investigator also holds responsibility.	This section has been deleted and reflected elsewhere in the guideline.
5	**4.3 Relevance of animal models** In this part it should be specified that the animal model not only should be relevant, but should also have the relevant targets.	This section has been deleted and reflected elsewhere in the guideline.
5	**6. Non-clinical aspects** For the tabulated summary of relevant non-clinical data a template should be provided. CHDR has a template and it willing to share this. This tabulated summery should be included in the Investigator Brochure. In addition, there should be a separate heading in this paragraph advising on what to do when there is no relevant animal model.	A specific template has not been provided to allow for flexibility.
5	**6.3 Pharmacokinetics** This paragraph states that PK in animals is mandatory data, however estimation of PK in humans also benefits from *in vitro* studies. It should be a possibility to quantitatively estimate human PK based on *in vitro* data, using PKPD modelling. This is also stated later on in the document, but should be replaced to this section.	The use of PK/PD modelling is included in the current guideline.
5	**6.5 Toxicology** “Serious toxicity should lead to a more cautious approach when setting doses in the FIH/early CTs.” What is a more cautious approach? Specification is needed here.	Text amended to reflect caution in terms of carefully considered and adequately justified approaches to applying risk mitigation strategies in the clinical setting.

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5	**7.1. General aspects** This section states that emerging data should be taken into account in line with pre-specified decision criteria. Unfortunately the recommendations how and when this should be performed are lacking. We suggest: data from the clinical trial should inform on safety, pharmacokinetics and pharmacodynamics and should be used in decisions about dose escalation in a following cohort. In addition it is often not possible to pre-specify exposure in a CT as described in lines 345-346. Decisions on tolerable exposure levels can also be made based on emerging data. Therefore, here it should be written that pre-specified should be done in cases where this is possible, but could also be done based on emerging data.	It is reflected throughout the guideline that pre-specification should be done where possible but can also be done based on emerging data.
5	**7.4. Maximum dose and dose range** Line 432 states that a trial design using a MTD approach is considered to be unethical for healthy volunteers. But line 429 states that in patients the MTD should not be crossed. But how will you know what MTD is? What could be meant, is that you could find the MTD by chance. In general this part should be re-written to be more specific and because of its importance it should be moved to the beginning of 7.4. It should also include exceptions, such as cytostatic agents.	The issue of maximum dosing was extensively commented upon and the relevant text has been amended throughout the document accordingly.
5	**7.5. Moving from single to multiple dosing** The order of this section is not logical and should be reconsidered. Also MTD is mentioned again in line 442. This illustrates that text around MTD should be very specific to avoid misinterpretation.	The issue of maximum dosing was extensively commented upon and the relevant text has been amended throughout the document accordingly.
5	**7.7 Patients** The order of this section is not logical and should be reconsidered. It should also be reconsidered if this part is relevant, because it is not very specific. It is advised to use this section to recommend sponsor and investigator to	Agreed. Text amended.

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	specify where/how patients are different from healthy subjects.	
5	**8.2.3. Choice of subjects** This list is not complete. Also differences in detail per bullet and specification is needed. For example line 537, in principle every patient has the possibility to benefit from other products or interventions. Another example is line 539, in principle patients are not allowed to be in more than trial at the same time.	Partly agreed. Text amended.
5	**8.2.6. Precautions to apply between treating subjects within a cohort** This section is contradictory. In first section (575-578) sentinel dosing is proposed for all cohorts, but in the last section (590-593) sentinel dosing may be appropriate at later stages in the study design (so not all cohorts). We agree that sentinel dosing should be done with the first administration of first in humans studies and in special cases as described in line 590. If these cases are not applicable, we don't think sentinel dosing is necessary.	The issue of sentinel dosing was extensively commented upon and the relevant text has been amended throughout the document accordingly.
5	**8.2.10. Stopping rules** In first in human studies it is impossible to know all criteria beforehand. This information will be gathered during the clinical study. There are always possibilities for stopping the study, besides what is described in this section. This makes this section vague and incomplete. In addition stopping rules could generate false security. Finally the safety for individual patients is always assessed by the PI. This should therefore be predefined in that way.	Stopping rules were extensively commented upon and the relevant text has been amended throughout the document accordingly.
5	**8.3. Documentation of sponsor and investigators responsibilities** There is nothing against describing the responsibilities of the sponsor and investigator(s) in decision making in the protocol, but we don't agree with the last sentence (line 726). This is only applicable for Data and Safety Monitoring Boards. Single-center Phase I and II clinical trials generally do not need a DSMB, since the local investigator will have access to all data. The clinical team follows the protocol and the dose decision is made by the principle investigator. In this case the decision team should be involved to make a rational decision (in line with the protocol).	Not agreed. It was felt important to include this requirement.

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5	**8.4. Investigator site facilities and personnel** First of all, not all clinical trials are executed in hospitals, therefore hospitalisation in line 734 should be changed to inpatient care. Second, you should have a procedure for acute emergencies instead of arrangements with the nearest IC unit. By Dutch law (but probably also in other countries), we cannot make arrangements to keep empty beds or reserve beds in the IC unit our nearest hospital. If there is an acute emergency, the local authorities decide to which IC unit the subjects should be brought and the appropriate IC unit will be informed.	Agreed. Text amended as proposed.
6	LEO Pharma appreciates the possibility to comment on 'Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products' (EMEA/CHMP/SWP/28367/07 Rev. 1). Our general and detailed comments can be found below. The common tone throughout the guidance that strategies should be science-based and decisions scientifically justified also on a case-by-case basis is much appreciated.	General agreement.
6	For the timing of evaluations and approvals for substantial amendments there might be a need for clear alignment with other guidelines (lines 410 and 446).	The issue of substantial amendments was extensively commented upon and the relevant text has been reviewed throughout the document accordingly. An algiemnt with other guidelines is considered outside the scope of the current scientific guide.
7	I believe a policy which excludes or markedly limits normal volunteers is important. There can be no benefit and, of course, potential harm. See the Belmont Report April 18, 1979.	This is considered outside the scope of the current scientific guide.

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8	The goals of this guidance are to: (1) establish a consistent terminology for discussing the starting dose; (2) provide common conversion factors for deriving a human equivalent dose (HED); and (3) delineate a strategy for selecting the MRSD for adult healthy volunteers, regardless of the projected clinical use. For following this indication we need to consider that the selection of a **PAD** depends upon many factors and differs markedly among pharmacological drug classes and clinical indications; however, once the MRSD has been determined, it may be of value to compare it to the PAD derived from appropriate pharmacodynamic models. If the PAD is from an in vivo study, an HED can be derived from a PAD estimate by using a body surface area conversion factor (BSA-CF). This HED value should be compared directly to the MRSD. If this pharmacologic HED is lower than the MRSD, it may be appropriate to decrease the clinical starting dose for pragmatic or scientific reasons. Additionally, for certain classes of drugs or biologics (e.g., vasodilators, anticoagulants, monoclonal antibodies, or growth factors), toxicity may arise from exaggerated pharmacologic effects. The PAD in these cases may be a more sensitive indicator of potential toxicity than the NOAEL and might therefore warrant lowering the MRSD. A strategy has been proposed to determine the **maximum recommended starting dose** for clinical trials of new therapeutics in adult healthy volunteers. In summary, usually NOAELs from the relevant animal studies should be converted to the HEDs using the standard factors outlined in FDA guideline (..). Using sound scientific judgment, a safety factor should be applied to the Human Equivalent Dose (HED) from the most appropriate species to arrive at the Maximum recommended starting dose (MRSD). This process means to define the upper limit of recommended starting doses and, in general, lower starting doses can be appropriate. The process described in this guidance should foster consistency among sponsors and Agency reviewers. The objective of a phase I trial is to determine the appropriate dosage of an agent or combination to be taken into further study and to provide initial pharmacologic and pharmacokinetic studies. It is generally assumed, at this stage of testing, that increased dose is associated with increased chance of clinical efficacy. Therefore, the phase I trial is designed as a dose-escalation study to determine the maximum tolerable dosage (MTD), that is, the maximum dose associated with an acceptable level of dose-limiting toxicity (DLT--usually defined to be grade 3 or above toxicity, excepting grade 3 neutropenia unaccompanied by either fever or infection). This MTD is then taken into further	The issue of starting dose was extensively commented upon and the relevant text has been amended throughout the document accordingly.

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	testing. Since evaluation of efficacy is generally not the objective of a phase I trial, it is not necessary to restrict to a patient population homogeneous with respect to disease, or even to restrict to patients with measurable disease (for which tumor response is determinable). It is important, however, to exclude patients with impaired organ function, who may therefore be more prone to serious toxicity. The fundamental conflict in phase I trials is between escalating too fast, so as to expose patients to excessive toxicity, and escalating too slow, so as to deny patients the opportunity to be treated at potentially efficacious dose levels. Toxicity as a function of body weight or surface area is assumed to be roughly constant across species. The initial dose for the phase I trial is taken to be 1/10 the MELD10 or, if smaller, 1/3 the LD10 (associated with 10% lethality) in the beagle dog. The use of a second species has been shown to be necessary, since in approximately 20% of approximately 90 reviewed drugs, mouse data alone was insufficient to safely predict the human MTD . The next problem is to define dose increments for the subsequent dose levels, and it is here that the various phase I trial designs part company. Many Authors suggested that dose escalation begin at the standard initial dose (usually the MELD10), and that it proceed, at most, one dose step at a time (although they did not give guidance as to how these dose steps should be defined). Others suggested that, rather than treat patients at the dose expected to yield the targeted rate of DLT (which gives 50% likelihood of exceeding the targeted MTD, according to the dose-toxicity model), patients should be treated at the dose associated with 25% likelihood of exceeding the MTD, according to the current state of the model, presenting simulations to demonstrate that this approach also avoided the increased DLT risk of the original CRM, while preserving efficiency and accuracy. Potter suggested, in answer to concerns about attempting to define an initial dose-toxicity model without clinical experience, that the initial stage of the phase I trial proceed in a standard fashion (escalating from the starting dose with successive 50% dose increments), until DLT is observed. At that point, a dose-toxicity model would be constructed, based on the trial data only. Patients would then be treated at the currently estimated MTD, based on the model. The trial would terminate when 18 patients had been treated, with at least 4 instances of DLT, and with at least 9 patients treated subsequent to the initial such instance. The design of clinical trial should be a Parallel Single- and Multiple – Dose.	

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9	Use of the term “cohort” not consistent and seems to imply always a “dose escalation”. This may not necessarily be the case. Cohorts can be done at same dose level, lower dose level or increased dose level. Suggest to clarify language and use consistently throughout document (+ reality is not matching current language in 8.2.5 – repeating same dose level *in case of meeting stopping rules at this dose level : no – but repeating it for other reasons should still be possible*)	Text amended in line with these and other related comments.
9	Often the word “should” is used allowing for a lot of interpretation still. Where the guidance would “require” something to be in place, suggest to replace the word “should” with “must”.	As this is a scientific guideline, the term ‘should’ is preferred.
10	Whole document: The terms “study” and “trial” should be used according to the definitions given in the new EU regulation on clinical trials (No 536/2014).	Agreed.
10	Section 2: The scope of the revised guideline has been extended from first-in-human (FIH) trials to early clinical trials in general. It is unclear whether the revised guidance with its recommendations refers to all early clinical trials. Guidance that refers to FIH trials only should be clearly pointed out. Furthermore, the guideline should be more precise to differentiate between specific aspects that need to be considered for NCEs and those to be considered for biologicals.	The scope applies to all FIH and early clinical trials and to all new chemical and biological products.
10	Section 4: A clear differentiation between targets that have already been addressed by compounds in FIH trials and completely novel targets should be introduced. In this respect, the resulting guidance for risk stratification should be delineated more stringently.	Text amended in line with these and other related comments. The concept of an uncertainty (risk based) approach has been introduced in this section and throughout the guideline.

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10	Section 5: A differentiation of the nature of the IMP (whether a biological or a chemical compound) should be incorporated. Variations in quality of the IMP and the resulting actions should be addressed. Consequences of changes or modifications in the manufacturing process should be evaluated and adequately communicated.	Not agreed. The scope applies to all FIH and early clinical trials and to all new chemical and biological products.
10	Section 8: Due to the very specific clinical and pharmacological as well as methodological knowledge needed for adequate evaluation of early phase trials, it is recommended that Ethic's Committees responsible for such trials have specific experience. This experience should cover the commonly applied trial designs with special focus on adequate selection of stopping and continuation rules including adaptive designs. Thus, there should be proven knowledge in early phase trials and clinical pharmacology.	Not agreed. This is considered outside the scope of the current scientific guide.
11	In general this guideline includes valuable recommendations which, when adhered to, enhance the safety of healthy subjects in the First-in-Human study and subsequent early clinical pharmacology studies. At the same time the guideline follows a pragmatic approach. We completely agree the emphasis the guideline lays on: – Determination of the selectivity of the IP (line 288). – The value of in vitro data for comparative animal and human PD (line 242). – Estimation of the anticipated therapeutical exposure using Pk/PD modelling (line 300). – The use of PK and available PD when escalating to a new cohort or new study part in a First-in-Human study (section 7.3. and 7.5). We think that searching for a Maximum Tolerated Dose should never be an objective of First-in-Human studies with healthy subjects. At the same time we think the dose limitation in the draft guideline is too restrictive: Instead of limiting exposure to the expected human therapeutic dose range (line 424) exploration of a	Text amended in line with these and other related comments.

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	supratherapeutic exposure, up to e.g. 5 fold above the highest anticipated clinical exposure, is needed to 1) better identify expected human toxicity in clinical practice and 2) evaluate e.g. QTc (according to Q&A ICH-E14) at supratherapeutic exposure levels, representing exposures during a perfect storm of e.g. drug-drug interaction and organ failure. Also, the exposure needed in patients cannot be fully predicted. Setting the exposure cap at the exposure reached at the NOAEL (line 684) is not necessary. For instance, if toxicity observed above the NOAEL is well monitorable, transient, not serious and/or species dependent. An exposure cap is needed in case of: 1) Irreversible or severe toxicity, especially without sentinel biomarker or 2) Risk of exceeding exposure in the GLP tox studies. Other major comments include: • Requiring that in- and exclusion criteria in general are in line with normal ranges (line 542) is scientifically unnecessary and not workable. • Not every SAE occurring should halt dosing in a cohort (line 587). Often, SAEs are clearly not related to the IP or study procedures. We suggest that only SUSARS should halt dosing in a cohort. Hopefully the above can be taken into consideration.	
12	Many of the proposed revisions in this draft guidance are either **inconsistent with the ICH guidelines** or add new expectations that exceed current ICH guidances (see comments on sections: • "6.1. Demonstration of relevance of the animal model – lines 244-284; • "7.2. starting dose" – lines 383-387) Unilateral revision of FIH regulatory requirements will create disharmony internationally. The recommendations on nonclinical safety studies outlined in ICH guidances have so far adequately addressed safety issues for first-in-human	It is stated the guideline should be read in conjunction with Directive 2001/83/EC and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations. Consistency with ICH was

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	and early clinical trials. **<u>Suggestions:</u> Fully align with ICH guidances**. Recommendations which are not in accordance with ICH guidelines should be discussed at ICH level to ensure international alignment.	considered in detail.
12	Most recommendations and examples provided in the guidance are applicable to biotechnology-derived pharmaceuticals but not to small molecules, although new chemical and biological IMPs are in the scope of the guidance (line 114). We believe that examples and recommendations need to be broadened to full cover the scope of the guidance.	The scope applies to all FIH and early clinical trials and to all new chemical and biological products.
12	We agree that a risk-based approach, which includes an integrative review of the mode of action, nature of the target, pharmacodynamics, and pharmacokinetic and nonclinical safety data, is useful in ensuring safety of healthy volunteers and patients in early clinical trials. However, the guidance is **overly prescriptive in the scientific aspects and principles required for regulatory submission** (see specific comments below). Each investigational medicinal product (IMP) is unique and the "one size fits all" approach for assessing potential risks associated with all IMPs is not appropriate. Thus, the guidance may lead to the unnecessary use of animals, to slow clinical development and, consequently, delayed access of beneficial medications to patients.	A statement is included in the introduction that as IMPs are widely different in their pharmacological features and intended use different parts of the guideline may be important for some and inapplicable to others.
13	**Section 5** Please add paragraph on the selection of the formulation, if applicable administration via infusion should be considered for first in human studies as administration can be easily stopped when needed.	Not agreed. Considered too specific a detail.
13	**Section 8.2.3** Please discuss characterisation of study subjects. To allow extrapolation of the first in human study PK data it is advisable to characterise included subjects carefully with respect to renal and hepatic function and metabolic and	Not agreed. Considered too specific a detail.

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	transporter characteristics.	
13	The word order and length of the sentences makes the guideline hard to read. Please check language and punctuation. Examples given in specific comments	Agreed. Text reviewed as proposed.
13	Words that come back very often throughout the guideline are some, such as, may etc. Please check in which cases the words can be replaced by a “stronger” word, to make the guideline more strict.	Agreed. Text reviewed as proposed.
13	**Please add references to literature where possible, and add a reference list. This would provide the rationale for the recommendations in the guideline and its scientific background.** (this is also in accordance with the PROCEDURE FOR EUROPEAN UNION GUIDELINES AND RELATED DOCUMENTS WITHIN THE PHARMACEUTICAL LEGISLATIVE FRAMEWORK, EMEA/P/24143/2004 Rev. 1 corr).	Agreed. Text reviewed as proposed.
13	The document contains many abbreviations. To improve readability please avoid uncommon abbreviations or abbreviations that are only common in a certain field of expertise.	Agreed. Text reviewed as proposed.
14	As stated by EMA in the November 15, 2016 Press release (EMA/731614/2016), one trigger for the current draft revision of the EMEA/CHMP/SWP/28367/07 guideline was the events related to the BIA 10-2474 study at BioTrial in Rennes. Fundamentally, the main issues in the BIA 10-2474 trial were associated with poor potency, poor selectivity and tissue accumulation. The revised guideline proposes new language regarding qualification of the primary pharmacology of the IMP, along with emphasis on PK/PD and modelling approaches, which are all welcome (and highlight the main issues in the BIA 10-2474 trial as evidenced by the TSSC Report). However, while it is certainly agreed that one must learn from serious incidents such as this (and the previous TeGenero trial), guidelines should also strive to be general and widely applicable. Some aspects of the proposed revision appear to be attempts to directly respond to the BIA 10-2474 case, i.e. the emphasis on sentinel dosing, the markedly increased requirement for substantial amendments during FIH trials and stopping criteria based on NOAEL exposure. It is however doubtful if any of these proposed actions would have prevented the dramatic toxicities seen in the BIA 10-2474 trial (as opposed to a more stringent scientific approach to the primary pharmacology). The reporting deficiencies have been discussed	Partly agreed. While the exact proposed structure has not been implemented, the concenpt of an uncertainty (risk based) approach has been introduced in this section and throughout the guideline.

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	extensively in the IGAS report. The proposed revision is intended to “further assist sponsors in the transition from non-clinical to early clinical development”, although the main new items as compared to the current guideline represent prescriptive measures (e.g. stopping rules based on NOAEL exposure; basing dose escalation decisions on a single individual). It is also difficult to see how a markedly increased use of substantial amendments would directly improve subject safety (the BIA 10-2474 trial a case in point). A more efficient approach would be to emphasise the need for a weight-of-evidence approach, taking into account all available data in defining starting doses, dose escalation approaches, stopping criteria etc. This would also go hand-in-hand with the proposed use of modelling and PK/PD methods. The proposed changes regarding stopping rules appear to be poorly aligned with the statement in the Introduction: “Strategies for development of a new medicine and the experimental approaches used to assemble information relevant to the safety of CTs should always be science-based, and decisions should be made and justified on a case-by-case basis.” Intra-subject dose escalations are not discussed in the revised guideline; the practice of “recycling” subjects from an earlier cohort to take part in a dose escalation is still common, but must be considered an unnecessary risk and should not be the norm – exceptions could be situations with cross-over food-effect assessments in the same subjects, as this generally takes place once the dose level has been judged safe and well tolerated.	
15	**Maximum dose/concentration in the FiH studies** It is mentioned that in general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified. The objective of any FiH study is to obtain information on exposure well above the exposure at the expected therapeutic dose in a healthy population to cover the impact of e.g. drug-drug and drug-food interactions, genetically impaired metabolism and organ dysfunction. This information is essential to support a safe conduct of subsequent early patient studies as well as DDI and TQT studies. Limiting exposure in the FiH will increase the risk in the subsequent early development studies where higher exposures might then be achieved with yet unknown safety in a more complex setting (e.g. co-administration with another drug and outpatient setting). The FiH studies in healthy volunteers are also done under carefully controlled conditions	Partly agreed. Text amended in line with these and other related comments (see above).

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	ensuring safety of the subjects. We propose that it will be clearly defined in the guidance that exploration of a wide concentration range, exceeding the expected human therapeutic dose range, is an essential part of the early studies in humans. Safety of the subjects will be guaranteed by ensuring that an appropriate risk minimization strategy is included in the protocol. **Standard use of MABEL** The draft guidance suggests that the MABEL approach should be followed for all compounds. There is no rationale for this requirement, because small pharmacologic effects of a low-risk compound should not be considered adverse. It is acceptable to start with doses that may have minimal human pharmacological activity and thus skip the very low dose levels, dependent on the properties of the compound. It is not needed to request that the MABEL approach is followed for all compounds, only when justified, e.g. for high risk compounds. **Starting dose and maximum dose/exposure** These are contradictory statements on the need of pre-specified dose and/or exposure levels: • *The starting dose and estimated exposure levels chosen for all cohorts and study parts should be pre-specified and a justification for these steps should be outlined in the study protocol.* • *……. and the corresponding doses with the expected exposure for each cohort should be stated in the protocol.* • *The dose increment between two dose levels should be guided by the dose/exposure-toxicity or the dose/exposure-effect relationship defined in non-clinical studies and by emerging clinical data.* This should be standardized in such a way that in a protocol a starting dose and a maximum dose or exposure will be defined. Intermediate dose levels can be given as example dose levels in the protocol. The actual intermediate doses will be guided by the dose/exposure-toxicity or the dose/exposure-effect relationship defined in non-clinical studies and by emerging clinical data.	

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	Sentinel dosing The section (8.2.6. Precautions to apply between treating subjects within a cohort) lacks clarity on when the use of sentinel subjects is recommended, including which cohorts and study parts. The text in lines 590-593 ("This approach may also be appropriate at later stages of study design, e.g. on the steep part of the dose response curve…") suggests that sentinel subjects are not compulsory for all cohorts, but seems to contradict the statement on line 575: "… first dose in any cohort …" We recommend the guidance make clear that use of sentinel subjects should be case-by-case and program driven, with appropriate justification (e.g. high level of precedence and known or benign pathway). **Use of substantial amendments** The frequent reference to use of substantial amendments to provide additional information to support study continuation has the potential to markedly and unnecessarily slow FIH studies in situations where the risk is considered low. Clearly laying out stopping criteria and dose escalation criteria in the FIH protocol allows clinical trials to proceed smoothly without the need for an amendment. In most cases, emerging PK, safety, and tolerability data can be utilized to make real-time adjustments to the dose, within predefined escalation limits and exposure caps, without the need for onerous substantial amendments. If the intent of the guidance was to imply substantial amendments should be submitted if there is a change to the predefined criteria for dose selection or changes to the predefined exposure cap, then this would be a reasonable. However, the guidance should be explicit that substantial amendments for dose escalation or progression to MAD are needed only when the study plan goes outside the predefined and approved plans. Lines 400-402 appear to suggest that planned dose levels may be adjusted without a substantial amendment.	
17	There isn't yet in the public domain any definitive information from the French authorities concerning the root cause of the disaster that occurred in the Bial clinical trial at Biotrial in Rennes. It would surely be premature to publish the new EMA Guideline until it can incorporate an appropriate response to that disaster.	Not agreed. The rationale for revising the guideline at the current time was laid out in the concept paper published 21 July

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		2016.
17	The recommendations given in the draft guidance for sentinel dosing are unclear. Many first-in-human SAD protocols specify use of sentinel subjects for the starting dose, but not for subsequent dose levels. Using that approach, dose escalation in SAD trials has an excellent safety record, and it should be possible to allow dose *escalation* after the first dose without use of sentinel subjects if that can be justified. It's unclear whether the Guideline recommends sentinel dosing in MAD studies. Since we don't yet understand what went wrong in the Bial trial in France, it's too soon to change established practice, which, with the exception of the Bial trial, has an excellent safety record. Requiring sentinel dosing at every dose level in a MAD study would substantially increase the time needed to complete early clinical trials, and delay patients' access to a potentially useful new medicine. Sentinel dosing should be considered, but should not be a requirement.	Text amended in line with these and other related comments on sentinel dosing.
17	We agree that a MTD approach in healthy volunteers, in which the dose is escalated until tolerability becomes unacceptable, is unethical. However, we don't agree that the expected human therapeutic dose range should not be exceeded in healthy volunteers. The expected therapeutic dose range is often not defined reliably during early clinical trials, so we don't know what therapeutic exposure might be. PD measures in healthy volunteers are rarely good enough to determine therapeutic exposure in patients. A margin is required to gather further data at higher plasma concentrations that might occur in patients. Also, supra-therapeutic doses are required in high precision QT studies, which are increasingly done early in clinical development.	Text amended in line with these and other related comments on maximal dosing.
17	The Guideline implies that PK and PK/PD modelling of non-clinical data yield reliable estimates of PK and PK/PD relationships in humans. That is often not the case. The starting dose level in a first-in-human SAD study is always specified, but subsequent doses are typically based on review of the emerging data, and are limited by pre-specified rules. In some places, the guideline seems to require sponsors to pre-specify every dose level/exposure level to be tested, and to submit a substantial amendment should the planned dose levels need to be adjusted; that would be unnecessarily cumbersome, and indeed the Guideline elsewhere refers to pre-specifying a dose escalation *strategy* as an alternative. It should be possible to incorporate	Text amended in line with these and other related comments on dose selection.

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	dose escalation rules in the protocol, without specifying every planned dose level.	
17	Use of the term 'cohort' is unclear and potentially misleading. Some parts of the guidance imply that a cohort is a *treatment regimen* (dose level), but in protocols for early clinical trials 'cohort' usually means simply *a group of individuals*. However, the terms 'group of individuals' and 'dose level' are not interchangeable if the trial design is a crossover or partial crossover. SAD studies may be parallel-group, complete crossover or partial crossover in design. In complete or partial crossovers, subjects in one cohort (group) may receive several different treatments (dose levels).	Agreed. Use of the term cohort was clarified in the final document.
17	There are several references to discussion and justification of trial-specific factors in both the IB and the protocol. Where details are trial-specific, eg starting dose or safety factors, the information should be presented in the protocol, not in the IB. The IB is not trial-specific, and may well be used to support subsequent studies.	Agreed. Text clarified.
17	The term 'repeated dosing' is preferable to 'multiple dosing'. Please apply that change throughout the document.	Not agreed. 'Multiple' is the commonly used term.
18	EUCROF welcomes the opportunity to provide comments on the European Medicines Agency's *'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products'* (EMEA/CHPM/SWP/28367/07), issued for public consultation. A number of our members routinely design and conduct first-in-human and early phase clinical Phase I studies with integrated protocols and are pleased to see the guidance updated to reflect current practice. In the revised guideline we have noted inconsistency with respect to the use of the terms "dose" and "exposure". We appreciate Lines 93–95 state, "Therefore, whenever dose is mentioned in this guideline, the expected exposure at that dose should always be taken into consideration." However, we would propose the use of the term "predefined maximum exposure" rather than "predefined maximum dose" as particularly in first-in-human trials dose is predicted during escalation and hence until a dose : exposure relationship is established in humans, best practice is to use exposure as justification (based on non-clinical data) with accompanying control measures. Any planned dose set	Agreed. A statement was added in the introduction that whenever dose is mentioned in this guideline, the expected exposure at that dose should always be taken into consideration

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	based on predictions has the potential to result in exposure that deviates from that which is expected. Hence switching between dose and exposure in this guidance could be confusing.	
20	Although IQ welcomes the Agency attempt to revise the guidance in light of current Industry practice, it is very concerned that the proposed revisions are overly prescriptive, inflexible and will result in a considerable increase in the duration and cost of first in human trials and other early CTs without a meaningful increase in clinical safety. Trying to make the guidance suitable for small molecule products, biological products, oncologic products, pediatric products and others product categories etc. that have specific study designs and different risk benefit considerations is challenging and this draft guidance appears not to have met this need. Of particular note, interpreting how this guidance applies to FIH CT studies in oncology patients is difficult and confusing. For example, ICH S9 Q&A step 2 document suggest that the use of MABEL in starting dose considerations for oncology products."should be considered if risk factors are derived from knowledge regarding (1) the mode of action,(2) the nature of the target, and/or (3) the relevance of animal models" rather than the routine/default usage as proposed in starting dose section of this guidance. The routine use of MABEL for all oncology products is particularly unwarranted and would result in many patients achieving no practical benefit due to the conservative approach that over weights safety. Similar concerns apply to other severely debilitating diseases that have analogous risk benefits considerations to oncology products. There are also many questions around application of this guidance to combination products, pediatric studies and studies in other special populations. As implied in the Scope (114-116) this guidance does not apply to an 'advanced therapy' but there is no definition as to what this means. Further clarification is warranted for what 'advanced therapy' consists of and whether this guidance applies to special populations (e.g., pediatrics). In addition, it is unclear whether vaccines (therapeutic or preventive) are in or out of scope? IQ recommends that the EMA clearly state what types of modalities are within scope, whether the guidance is applicable to combination therapies, advanced medicinal therapies and vaccines etc. It would also recommend that patient populations like pediatrics, oncology and patients with other severely debilitating diseases be out of scope for the revised guidance. The following comments summarize the most important concerns identified by IQ members. These issues include recommendations that are unclear or have the potential to negatively impact the typical efficient and thoughtful	Text amended in line with these and other related comments. A statement is included in the introduction that as IMPs are widely different in their pharmacological features and intended use different parts of the guideline may be important for some and inapplicable to others.

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	progression of innovative compounds through first-in-human (FIH) and into patients by applying a broad recommendation for issues that should be considered on a case-by-case basis. • **Alignment with Existing ICH Guidance** IQ member companies conduct nonclinical studies in support of first in human clinical trials in accordance with ICH guidance. Many of the proposed revisions in the EMA guidance are inconsistent with current internationally agreed upon ICH guidances, in particular ICH M3, ICH S6, ICH S9Q&A, and as a result will lead to confusion and lack harmonization across ICH regions. In the context of ICH M3 there is a major concern with a number of statements in the revised draft document that are not aligned with ICH M3 principles. This mainly concerns: (1) Dose setting (2) Overemphasis put on PD effects (3) Some of the stated principles might not be as such applicable to all types of molecules in scope of this guideline. There seems to be a mix up of approaches more appropriate for specifically biologicals (aligned with ICH S6) with those more appropriate for small molecular entities ((aligned with ICH M3 (R2)). Overall, given the conflicting recommendations with existing ICH guidelines and the proposed additional regulatory requirements, we strongly recommend that EMA follow an ICH process for guidance revision, rather than undertake unilateral revision of FIH regulatory requirements. • **Starting Dose** The recommendation regarding determination of starting dose, as outlined in Section 7.2, is unclear. It appears the recommendation is to use exposure at the NOAEL or MABEL to estimate human equivalent dose, then apply a safety factor. This strategy is different from FDA guidance, which recommends conversion of the NOAEL dose to human equivalent with a scaling factor (i.e. based on body surface area etc.), then application of a safety factor. Greater clarity is needed on what exactly is being recommended. Further, and perhaps most importantly, we do not agree the use of MABEL is appropriate for limiting the starting dose in all cases. The decision to utilize a MABEL or PAD approach rather than the NOAEL should be risk-based and the use	

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	of MABEL for selection of starting dose may be overly conservative in many situations where the NOAEL approach would be adequate, particularly if an additional safety factor is to be applied to the MABEL. MABEL should be calculated and considered in the starting dose depending on the anticipated biologic effects, and an additional safety factor for MABEL should only be applied under very specific conditions (e.g. in cases where anticipated exaggerated pharmacological effects might induce serious effects and where there is a serious concern that predictive models are not sufficiently reliable regarding the pharmacologically active range in humans or when a steep dose-response curve is anticipated). We are concerned that expectations for an elaborate pharmacology model in the end will not add value to the assessment and may overly complicate the process. The original guidance was clearer in specifying when the use of MABEL rather than NOAEL should be considered: “For investigational medicinal products for which factors influencing risk … have been identified …the ‘Minimal Anticipated Biological Effect Level’ (MABEL) approach is recommended.” It would be helpful if the EMA could expand on its rationale for recommending the MABEL approach in addition to the NOAEL for small molecules, as it is the experience of the IQ that the current approach is sufficient to ensure safety of the FIH starting dose. Nor does the TSSC review of the Bial incident indicate selection of starting dose was a contributing factor. In summary, IQ members strongly support an appropriate and risk-based approach to the use of MABEL or PAD rather than its use by default. • **Maximum Dose and Dose Range** We strongly disagree with the proposal that the expected human therapeutic dose should not be exceeded in studies of healthy subjects as a general principle. There are indeed instances where this is the case, depending on the safety margin and the anticipated therapeutic window, but in general, it is a key goal of the FIH study to define PK and safety/tolerability at doses and exposures that are higher than the predicted therapeutic dose range. Furthermore, given the intensive monitoring that is part of FIH studies, we believe that the phase 1 (FIH) studies provide the appropriate environment for exploration of safety and tolerability of a molecule. Such information is essential to subsequent clinical development in which higher exposures may be observed in patients due to normal variability, comorbidities, and concomitant medications (i.e. DDIs). In addition, the predicted therapeutic dose range at the time	

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	of FIH conduct is based on translational PK/PD data, often preclinical disease models or in vitro data that do not directly mimic the human disease, and which is always to be adjusted on the basis of clinical efficacy findings in Phase 2b/3. Rather than focusing on the predicted (i.e. derived from preclinical data) exposure levels related to PD (with or without adverse effects) the risk assessment should focus on the (severity, reversibility and monitorability of) anticipated adverse effects due to (exaggerated) pharmacology or toxicity. The proposal that the human therapeutic dose should not be exceeded in studies of healthy subjects as a general principle is also in our view inconsistent with ICH principles. Under conditions that the package of nonclinical studies meets the general ICH M3(R2) recommendations, the maximum clinical dose can be based on standard risk assessments. Given that observed toxicities/adverse effects in animals are monitorable, reversible and clinically manageable, as stated in ICH M3(R2), higher exposures above the most relevant NOAEL established in the enabling toxicity studies can be supported. Therefore we consider that the following lines are not supporting previously agreed upon (ICH) principles: • 424-425: "*In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified*." • 683-685: "*A dose stopping criterion of the clinical exposure (Cmax or AUC) equivalent to the exposure achieved at the NOAEL determined in the most sensitive non-clinical species, adjusted by safety factors if appropriate and based on available PK data, should be included.*" Overall, IQ member companies believe that there is rarely a safer opportunity to explore higher exposures to support later stage clinical development than in the FIH study, where subjects are in an intensively monitored environment. It is well understood that dosing should cease if safety or tolerability or exposure limits are reached (whichever occurs first), but without exploring the safety of a relatively broad range of exposure it will be difficult to anticipate the impact of exposure variability in a much larger set of patients. Furthermore, while the above considerations should be seen in the context of reaching a plateau in pharmacology, when there is absence of a validated biomarker of target engagement, it is important to account for the potential uncertainties in the predicted efficacious exposure.	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	• **Stopping Rules Based on Individual Subject Exposure** The recommendation to consider the maximum clinical exposure in an individual subject is not practical nor appropriate for dose-limiting escalation based on stopping criteria defined based on non-clinical data. To begin with, the exposure maximum is typically defined by mean animal exposure (or a fraction thereof). Further, it is unclear how such an approach would be implemented practically. Would the outlier in every dose cohort need to be considered in projecting the maximum exposure at the next dose level, or would an average variability across the completed cohorts be considered in the projection? Dose escalation might be prematurely and inappropriately halted based on the exposure of 1 subject with aberrant PK results in a relatively low dose cohort. Please consider revising to indicate that in addition to average (and %CV) exposures within a cohort, individual PK data should be taken into consideration for decision-making on dose escalation. • **Substantial Amendments During FIH** The frequent reference to use of substantial amendments to provide additional information to support study continuation has the potential to markedly and unnecessarily slow FIH studies in situations where the risk is considered low. Clearly laying out stopping criteria and dose escalation criteria in the FIH protocol allows clinical trials to proceed smoothly without the need for an amendment. In most cases, emerging PK, safety, and tolerability data can be utilized to make real-time adjustments to the dose, within predefined escalation limits and exposure caps, without the need for onerous substantial amendments. If the intent of the guidance was to imply substantial amendments should be submitted if there is a change to the predefined *criteria* for dose selection or changes to the predefined exposure cap, then this would be a reasonable. However, the guidance should be explicit that substantial amendments for dose escalation or progression to MAD are needed *only when the study plan goes outside the predefined and approved plans*. Lines 400-402 appear to suggest that planned dose levels may be adjusted without a substantial amendment. • **Requirement for an evaluation of the mechanism of toxicity and or cause of death (including**	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	histopathological evaluation) for all mortalities and/or serious toxicity in nonclinical studies. Line 329 indicates that …"If mortalities and/or serious toxicity are observed in nonclinical studies, an evaluation of putative mechanism of toxicity and/or cause of death is expected to be addressed (e.g. consideration of histopathological examination of deceased animals, which is certainly necessary in pivotal studies and should also be considered for dose range finding studies)." IQ members do try to identify cause of death where feasible as outlined in our response to line 329. The request to evaluate the "putative mechanism of toxicity" in all instances could vastly increase the number of animals/studies in support of CTAs and may unnecessarily delay a CT when uncertainties can be mitigated clinically. If several target organs are identified then several experiments per target organ may be necessary. Determination of any mechanism of toxicity is a lengthy process that can take years and can be inconclusive. • **Overall Summary** IQ continues to believe there is not a "one size fits all" approach that can be adapted to early CTs and supports the adoption of a risk-based approach with application of additional safeguards and risk mitigation measures appropriate for the target and molecule under investigation, and the human population (healthy subject or patient population) enrolled in the CT. The overwhelming evidence from publications on the safety of first in human (phase 1) trials, with very few exceptions, continues to support the view that they are generally safe with very few severe or serious adverse events (Bonini et al 2016, Johnson et al 2016 and Emanuel et al 2015). Bonini S, and Rasi G. (2016). First-in-Human Clinical Trials — What We Can Learn from Tragic Failures. N Engl J Med 375:1788-1789. Emanuel JE, Bedarida G, Macci K, Gabler N, Rid A, and Wendler D. (2015). Quantifying the risks of non-oncology phase I research in healthy volunteers: meta-analysis of phase I studies. Br Med J 350:h3271. Johnson RA, Rid A, Emanuel E, Wender D. (2016). Risks of phase I research with healthy participants: A systematic	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	review. Clin trials 13(2):149-160.	
21	EUCROF's Early Phase Working Group welcomes the opportunity to provide comments on the European Medicines Agency's *'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products'* (EMEA/CHPM/SWP/28367/07), issued for public consultation. In our response we draw on the group's experience of designing and performing integrated early phase trials from First in Human to Proof of Concept in healthy and patient participants for more than a decade. The majority of our comments focusses on the following key areas: • Consistency and applicability of the terms "dose" and "exposure" in the guidance; • The setting and application of dose escalation rules, study progression and toxicity rules, including minimum data requirements for decision making; • The overall aim to maintain and further enhance the benefits of integrated adaptive trials, such as time and cost-efficiencies, science-based decision making and safe risk management processes.	General comment.
22	PAREXEL welcomes the revision of the guidance since it improves considerably the conduct of early clinical research. The following reflects scientific advances in translational medicine during the last decade: - Decisions during early clinical development are based on exposure and not on dose - Integrated protocols are accepted with possible overlap of study parts, which improve scientific quality - Clear definitions of flexibility in study conduct - Requirement of substantial amendment when predefined criteria are not met for the emerging data Some elements included in the revision may need rephrasing, as these are ambiguous or leave room of interpretation (see below line by line comments).	Text amended in line with these and other related comments.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	Non-clinical aspects: This FiM guidance update contains additional requirements in a number of areas that are not covered by the current ICH guidelines for non-clinical development. It is important to insure that any proposed changes are based on scientific evidence that these changes would contribute to benefit/risk assessment. It is suggested the ICH guidelines need to reflect the proposed changes in future ICH updates otherwise it may be a barrier to cross-regional early development performed in EU in the future without any potential benefit to trial subject safety. It is noted that the proposed guideline revision is focussed on documentation to be provided in the IB and Protocol (IMPD is not mentioned anywhere). - From a practical point of view it is preferable to have a 1:1 correspondence between IB and IMPD requirements for non-clinical information, to allow flexibility in submission strategy. What steps are taken to align IMPD guidance? - The section on Quality aspects lack precision with respect to what should be presented where – the IB [per ICH E6(R2) guidance] does not foresee detailed formulation documentation in the IB, (nor in the Protocol) and this is also not ideal from an IP perspective. If detailed general requests on non-clinical Pharmacology and PK documentation are introduced for FiM studies in EU, they need to be harmonised with the IMPD guidance, and should ideally be aligned to other regions via ICH in order not to stall cross-regional development. **Dosing selection, planning and conduct:** The general approach to emphasise integrated assessment is laudable. Especially secondary pharmacodynamic effects which have often been overlooked. However, the extension of MABEL/PAD determination to all new medicinal products (Line 364-387) lack clarity and precision. In contrast to the current guideline, where this risk mitigation measure is applied in clearly defined cases of increased risk, this lacks a clear scientific justification: - What is the scientific evidence base that a MABEL approach would have minimised trial subject risk for any	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	follow-on medicinal products in any pharmacological class to date? There must be scores of small molecule and biologics examples to substantiate or refute this assumption. - What is the evidence base that any first in human issue with a (reversible) antagonist would have been avoided by a MABEL assessment when NOAEL data in a relevant species was utilised? The following approach as outlined in Line 424 ("In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified.") is considered to be in contrast to the nature of early clinical development, i.e. to explore the dose/exposure-effect relationship with special attention to safety. The expected therapeutic human dose range may not always be known during the conduct of a FIH study and cannot be confirmed with certainty in such an early phase of clinical development. Additionally, it is required to explore safety implications of increased exposure in the development of a drug, e.g. to understand risks in DDI and thorough QT studies, where supra therapeutic dose or exposures are either expected or required, respectively.	
22	Please consider to avoid using and/or. Suggest to be replaced "or"…or… "both".	Agreed.
22	Please consider to avoid examples in brackets, since these might be interpreted as being exclusive.	Agreed.
26	The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 130,000 employees engaged in research activities around the world (including 57,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 7,000 clinical trials involving 1.3 million research participants in over 100 countries. On average, each of our member companies works with more than 700 research sponsors annually. ACRO welcomes and supports the draft guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. ACRO considers this to be a comprehensive document that provides sound, detailed guidance to enhance the	General agreement.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	safety of participants in these studies. In particular, ACRO welcomes: • The extension of the current guideline to cover early phase clinical trials with integrated protocols that combine a number of different study parts • The strong emphasis on risk identification and mitigation, and especially the recognition that all available information should be taken into account in reaching dosing decisions • The acknowledgement that using a maximum tolerated dose approach is considered to be unethical for healthy volunteers.	
27	Overall, most revisions to the guidance reflect best practices in early clinical drug development. However, as currently written the revised recommendations for dose escalation and stopping rules may have the unintended effect of preventing sponsors from exploring the full range of drug exposure enabled by preclinical safety studies. Without thoroughly exploring the tolerability of a new drug in Phase 1, an efficacious drug may be discontinued prematurely, or may fail later in development due to inadequate dose optimization. In addition, without exploring the full range of exposure and tolerability in Phase 1, the safety profile of a new drug may be inadequately defined prior to initiation of a larger study. Therefore, we suggest additional flexibility in the revised recommendations for dose escalation and stopping rules to facilitate safe and effective exploration of the full exposure range of a new drug.	Text amended in line with these and other related comments.
28	The Cell and Gene Therapy Catapult welcome the opportunity to comment on Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. We believe this revision is beneficial in principle, however we think that some aspect of the current text can gain in clarity for the benefit FIH clinical trial sponsors.	General agreement.
30	1. This is a helpful and useful document, with advances since the 2007 version that will improve the design of FIH/early CT studies. It is however very long and wordy. Use of bulleted lists for easy checking by the reader could enhance the value to the relatively inexperienced investigator. 2. The document lacks a statement in the Introduction (Section 1.0) concerning the purpose of FIH/early CT studies.	Text amended in line with these and other related comments.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	The introduction includes the statement: “The aim should always be the safety and well-being of the trial subjects, whether patients or healthy individuals”, but this is not an objective. Objectives are offered at various points in the main text (e.g. “assessment of tolerability, PD or PK profile” in Section 7.1 line 337, “maximum tolerated dose” in Section 7.4). It is important that the document states the objectives of these studies early in the introduction section. In particular, it should state that FIH/early CT trials provide the first opportunity to understand the pharmacology and effects of a drug in humans (i.e. human pharmacology). Safety is not the primary objective of these studies since this approach leads to the MTD being the primary outcome as is currently often the case. The document clearly states this: “A trial design using a MTD approach is considered to be unethical for healthy volunteers.” The fact that the MTD cannot be the primary aim of a study also needs to be here in the Introduction, rather than buried in the text. We have proposed changes to account for this. 3. The information on the ‘General aspects of planning and conduct of FIH and early clinical trials’ currently in Section 8 should comprise the introduction to the document and this should start with the requirement to state clearly what the primary and secondary objectives of the study are. There should then be a section on choice of study population i.e. healthy volunteers / patients including severity of disease, age, sex. This should then be followed by Sections 8.2 to 8.4. By doing this, the clinical study design and contents, together with the proposed risk minimisation measures sets the tone for the rest of the document. Following this with the Sections on Quality, the Pre-Clinical aspects and Dose Selection will then give a much more logical flow to what is presented and discussed. 4. The document indicates the fundamental importance of pharmacodynamic (PD) measures for the safe introduction of a drug into humans. In places, it clearly emphasises the need for PD outputs e.g.: “The choice of the subsequent dose levels should include some estimate of the potential PD effects …” (section 7.3, line 390-391).However, this is not consistent throughout the whole document. For example, in other parts of that section, only emerging clinical data is required to be considered for dose escalation. We have clarified that all emerging PK and PD data must be considered during dose escalation. The inclusion of PD measures should be given far greater prominence in the document. This should be combined with the development of a PK/PD model whenever possible.	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	5. The whole question of 'integrated protocols' needs a separate discussion starting with what is really meant/its definition. Inclusion of a fed / fasted crossover or a healthy elderly group at a particular dose is usually uncontroversial but 5 part studies involving single and multiple doses with various subgroups starts to become a blank cheque from the Regulator and Ethics Committee. Could the EMA provide guidance in general terms of what is reasonable to include in a single study and what is not? Section 8.2.2 really gives the guidance needed – it also should be presented at the beginning of the guidance. 6. The composition of the decision-making group (trial steering committee TSC) is very important to safe and effective trial performance. This is addressed within section 8.3 Documentation of sponsor and investigators' responsibilities on lines 723-727. The section should also include specification of what types of expertise and roles are required in the decision-making group in tandem with a guide to what training those sitting in a decision-making group should have. The inclusion of an independent person on the TSC would be beneficial to all involved in the study. The information is useful and warrants its own section as 8.4 (moving each subsequent section on by .1). Site facilities would then become 8.5, etc. 7. There is much overlap between Sections 4 (4.1 – 4.4) and Section 6 including 6.1 to 6.6. Most of Section 4 should be incorporated within Section 6 and Section 4 could then be deleted. After the introduction to Section 6, there should be a section stating that "In vitro quantitative data on receptor binding affinity, selectivity and reversibility require careful scrutiny with respect to desired and potential undesired effects. Quantitative data should be available in the Investigator's Brochure". 8. The words 'should' and 'must' are used in the document. It would be helpful if these terms were defined at the beginning of the document following the GMC's guidance on Good Medical Practice (http://www.gmc-	

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	uk.org/guidance/good_medical_practice/professionalism_in_action.asp). This could simply cite the text from the GMC: "In Good Medical Practice, we use the terms 'you must' and 'you should' in the following ways. 'You must' is used for an overriding duty or principle. 'You should' is used when we are providing an explanation of how you will meet the overriding duty. 'You should' is also used where the duty or principle will not apply in all situations or circumstances, or where there are factors outside your control that affect whether or how you can follow the guidance." 9. This guidance appears to be only directed at FIH and early phase studies in adults. This is not stated. If this is the case, it should be stated. If the EMA considers to exclude paediatric populations from this guidance, then this guidance should also reference a relevant EMA guidance for First-in-Children or early phase studies in children. 10. In the following comments, for clarity and simplicity, the revised text only is presented (without tracked changes). The text should be compared with the current version of the Guidelines sent out for comment (10 November 2016, EMEA/CHMP/SWP/28367/07 Rev. 1).	
31	The request for information/confirmation concerning the GLP status of pivotal non clinical studies is a very good addition to the guideline.	General agreement.
32	The Paul-Ehrlich-Institut acknowledges the update of the guideline.	General agreement.
33	Whole document: It is unclear whether some recommendations refer to first-in-human (FIH) trials only or all early phase CTs.	Defined in scope.
33	There is no differentiation between NCEs and biological products, or between novel targets and FIH trials in general.	Defined in scope.
33	Are microdosing or exploratory studies included in the scope of this guideline?	Specific reference is made to exploratory clinical trials and microdosing in the guideline.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
33	In various part of the proposed guidance the wording is too strong and conservative not allowing enough flexibility in the conduct of the CT e.g. systematic substantial amendment when dose escalation is modified or no overlap between sub-parts of the CT. In addition flexibility is needed when this is the basis of the design as in the Bayesian Continuous Reassessment Method in which final number of subjects/patients per cohort is not fixed and may be replicated.	Partly agreed. Text amended in line with these and other related comments.
33	Ethics Committees in charge of the review of such trials should have a documented knowledge in early phase trials and clinical pharmacology.	This is outside the scope of the current guideline.
34	First and most importantly, Alexion recommends the final guideline allow flexibility in the design of early human studies that is appropriate given the full profile of the IMP and other pharmaceutical products in a similar class and/or with similar modes of action, as well as the intended patient population. To aid in the evaluation of the IMP and acceptability of study designs, Alexion requests timely collaboration with the EMA that is supported by a systemic risk assessment as part of the IMPD evaluation. The goal of the systemic risk assessment is to ensure improved protection of human subjects by • amassing and evaluating all relevant data regarding the IMP and similar products, • better understanding and anticipating the potential safety profile of the IMP in early clinical studies, and • proposing appropriate clinical mitigation and monitoring strategies Importantly, the systemic risk assessment should include data *unavailable* to sponsors, such as nonclinical and clinical safety information shared with the EMA for similar competitor products. Alexion considers this systemic risk assessment important to ensure a thorough and complete evaluation of the IMP's potential benefit-risk profile and improved protection of human subjects in early clinical studies. Below is a proposed template that Alexion suggests be prepared by the sponsor, and either added to, or at a minimum, evaluated by the EMA, in the context of similar products for which EMA has additional information pertinent to the IMP under evaluation.	While the exact proposed structure has not been implemented, the concenpt of an uncertainty (risk based) approach has been introduced throughout the guideline.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	<table><tr><th>Reference (Study ID/publication/ HA correspondence)</th><th>Finding/Assumed Risk</th><th>Foreseen Risk in Humans</th><th>Risk Assessment (probability)</th><th>Risk Mitigation and Monitoring Strategy(ies)</th></tr><tr><td></td><td></td><td></td><td></td><td></td></tr></table>	
34	Second, Alexion requests the EMA provide additional clarity regarding the use of appropriate animal models in the nonclinical setting (e.g. knock-out, transgenic or humanized animals) in the translation of disease as it progresses over time, and the development and/or validation of clinical outcome measures, biomarkers and companion diagnostics.	Too specific detail.
34	Third, Alexion requests the EMA provide additional scientific guidance regarding the conduct of early human studies involving medicines that use novel formulation or delivery system(s) (e.g. nanomaterial, liposomes, micelles, emulations, etc).	A statement is included in the introduction that as IMPs are widely different in their pharmacological features and intended use different parts of the guideline may be important for some and inapplicable to others.
36	All the partners of the REGenableMED project are aware of the existence of this draft Guideline. We welcome the opportunity to review this 'Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products'. We welcome the clarity of this guideline, especially regarding its links with other existed documents (notably lines 114- 147).	General agreement.
39	The Club Phase I acknowledges that the proposed revised Guidance, is following several of the comments/proposals	Text amended in line with these and other related

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	we expressed during the first round of the revision. However we would like to highlight few point to comments (1) The strong wording regarding the limitation of the maximum dose in Healthy volunteers (Line 424-425) is misleading. In deed the SAD /MAD CT should provide relevant safety and tolerability data with doses beyond the intended therapeutic one. This supra-therapeutic approach should cover potential large population variability and more importantly should cover the worst case scenario exposure (e.g. drug-drug interaction, special population with chronic organ failure). In addition this supra-therapeutic doses would be aligned with the one described in the thorough ECG study of ICH E14 guideline. As we highlighted in the previous round of review we suggest to introduce this concept of supra-therapeutic exposure based on strong scientific rationale in which simulation from PBPK would be key (e.g. "X" fold the intended therapeutic exposure, "X" being 2 to 5) (2) Regarding non clinical aspect (§6) relevant data on off-target activities should be emphasized both qualitatively and quantitatively and not only for the parent compound but also for the metabolites, including reversible /irreversible interactions. By the way we are quite surprised that nothing is written in the current revised document on this extremely important point. (3) In various part of the proposed guidance the wording seems too strong and too conservative not allowing enough scientifically based flexibility in the conduct of the CT e.g. systematic substantial amendment when dose escalation is modified or no overlap between sub-parts of the CT. Flexibility is needed when this is the basis of the design as in the Bayesian Continuous Reassessment Method in which final number of subjects/patients per cohort is not fixed and may be replicated. In deed flexibility should more allowed than in the current proposal as soon as this is based on strong scientific and pre-specified rationale as well as rules. (4) Lastly consistency across the various section of the current document need to checked; it is sometime very confusing.	comments.
40	Several sections/paragraphs refer to the use of PK data and results to support decision making, but for some IMPs such as toxins, cell or gene therapy and some treatments involving proteins there is not PK available. In this case, the strategy be focussed on the other criteria of judgment such as safety and PD or is there specific guidelines for the IMP	A statement is included in the introduction that as IMPs are widely different in

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	without PK data/results.	their pharmacological features and intended use different parts of the guideline may be important for some and inapplicable to others.
40	The Guideline doesn't mention or gives room for special drug that need titration, a practice common for certain classes of drugs. Also, the Guideline seems to very really based on small molecules, which is still the majority of IND today, but very little is say to give relevant advices for the development of biological such as cell or gene therapy or even vaccines. Statements mentioning those cases should be made.	Addressed in scope of the guideline. Also a statement is included in the introduction that as IMPs are widely different in their pharmacological features and intended use different parts of the guideline may be important for some and inapplicable to others.
40	The Guideline is mainly about strategies to identify and mitigate risks for first-in-human and early clinical trials and on purpose highlight the necessity to leverage pre-clinical data for dose ranging and have data-driven decision making processes during the conduct of trials. However it is not mentioned or recommended the use of Bayesian statistics to mitigate risk and support decision making with appropriate and updated information during the conduct the trial. The Bayesian statistics is particularly suited for early phases also labelled learning phases because 1) it makes appropriate use of prior information –the preclinical and literature or scientific knowledge-, 2) it permits a continuous update of the knowledge (the posterior distribution) without loss of meaningfulness and 3) it provides naturally the predictive distribution of the future events which is at the heart of the Guideline: ensure it's safe for the next level or dose given cumulated data. Promoting methodologies such as Bayesian statistics that in essence carry-on correctly the	The use of Bayesian statistics is considered too detailed for the scope of the current guideline.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	uncertainties and has as key outcome the computation of risk would be a great added value.	
40	The Guideline is about defining strategies to protect the human volunteers or patients, but for that very purpose the use of a Model-based Drug development can have a great value to maximize the informative outcome of a trial and in the same time minimizing risks for subjects. Beyond recommendations for doses and dose ranging, the Guideline should emphasizes the fact that early phases trials are and should be a critical part of a global Model-based development strategy that operates in favour of ethic in research.	The use of models is considered too detailed for the scope of the current guideline.
40	Whilst the Guideline suggest that selection of doses and ways to conduct the trial should be duly documented and justified, it never mention the value of using simulations based on prior or preliminary data (to be used for justifying the dose range). Simulations based on those information would allow to evaluate upfront the effectiveness and value of the proposed rules and information. If the Guideline proposes to control risk and ensure safety of patients under weak information, then evaluating the operating characteristic of the various operational aspects given available information could be a valuable recommendation.	The use of simulations is considered too detailed for the scope of the current guideline.
40	The Guideline promotes the use of pre-clinical data and animal models to justify dose range, escalation strategies in order to minimize risks for patients. However the Guideline don't really propose or suggest strategies or recommendations to ensure that the data generated by the pre-clinical studies are having the level of statistical reliability (bias, precision) needed to support the decision and dose justifications. Pre-clinical studies used in a IND need to be documented according to GLP standards, but the performance of the pre-clinical studies should be evaluated and assessed the same ways (bio)analytical methods or bioassays need to be qualified. The reproducibility of those studies is becoming a known problem in the literature and proposing concepts such as in USP <1032-1034> guidance would be valuable.	Too specific detail for the scope of the current guideline.
41	This draft revision of the EMA's guidelines on FIH and early phase clinical trials represents a significant improvement on the previous version and is welcomed by the PISRC. The draft successfully addresses many of the shortcomings of the previous version and brings the guidance more up to date and in keeping with how early phase trial design has evolved in recent years. There are however a numbers of areas where further clarification or strengthening of the	General agreement.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	guidance would be beneficial. In particular, the move towards recognising the importance and implications of emerging PK and PD data in addition to clinical data is welcomed, but this principle could be emphasised further in places as detailed below.	
42	Recommend additional text regarding a deeper emphasis for prompt and transparent safety reporting to all applicable parties: • regardless of the cohort when adverse or serious adverse events are identified • additional emphasis on prompt information dissemination of safety updates to other volunteers and obtaining their consent to continue the trial (verbal in additional to written) • Immediate reporting of SAEs/SUSARs to Sponsor, Ethics Committees and Health Authorities	Text amended in line with these and other related comments.
42	In several sections, the Guideline details the need to document decisions, justifications, strategies etc., without clearly specifying where exactly this should be documented (e.g. in the Investigator's Brochure, the trial protocol, safety monitoring plan, clinical monitoring plan etc. [See for example comment regarding lines 149-151.] **Proposed change:** Please specify where the information is expected to be included and/or which alternative document would be appropriate.	Too specific detail.
43	**Comment 1** We have contributed for a large part to the EFPIA document with comments on this draft guideline, which you receive separately. The comments included below reflect our positions to aspects/text in the draft guideline not covered in the EFPIA version, or provide further detail on positions that are covered in the EFPIA version. **Comment 2** As also indicated in the EFPIA comments, it is important that the guideline acknowledges and differentiates the	Partly agreed. Text amended in line with these and other related comments.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	requirements for trials conducted in high-morbidity and high mortality disease states such as advanced stage cancers. The extent the guideline is intended to be applicable to such settings should be clarified. Currently, there is little differentiation between these and other disease areas in the guideline. Guidelines allowing for more flexibility in certain settings, e.g. ICH S9, are referred to in Section 3, but guidelines like ICH S9 are not covering all the aspects addressed in the current guideline under review. The special situation for studies in patients is only considered in sections 7.7 Patients (L. 454-469) and 8.2.3 Choice of subjects (L. 522-543). There are also no considerations on the choice of dosing schedules and on combinations (including novel-novel). In line with the above, we have presented comments relevant to studies in these conditions separately at the end of the document.	
44	The Alliance for Biomedical Research in Europe (BioMed Alliance) welcomes the EMA Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. Animal experiments are still indispensable for biomedical research aimed at establishing new options to generate diagnostic and therapeutic options for humans and to minimize the risk in first in human studies and early clinical trials. Both aspects result from the complexity of biological interactions on the molecular, cellular tissue and organ level in a living organism. Increasingly, experimental approaches are developed which use cells and multicellular arrays *in vitro* to model biological interactions and pertinent mechanisms for health and disease. Besides avoiding the necessity to use laboratory animals, these approaches have the advantage to provide a reduced level of relevant interactions and boundary conditions: they allow simpler testing and interpretation of results. Thus, they are optimally suited to identify targets and develop approaches for clinical treatments. However, the reduced complexity of reductionist experimental approaches also limits the scope of functions which can be addressed and renders the results less comprehensive with respect to possible risks in the clinical application. For example, if an *in vitro* model does not have a beating heart and blood circulation, respective effects and risks will not be apparent. Thus, to decrease the potential risk for patients, testing in a model which has all functional systems of a complete mammalian organism is mandatory. It is often criticized that results of animal experiments cannot fully predict reactions in human patients and thus will not be a 100% protection from risk in early clinical studies. But even between individual patients, there are very	Partly agreed. Text amended in line with these and other related comments.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	relevant differences in reactions and complications – which is evident from the large number of patients included in clinical trials. It is thus relevant to acknowledge that no single experimental approach can predict outcome in a given patient, and therefore a wide array of approaches ranging from *in silico* and *in vitro* approaches to clinical trials is required to minimize the risk and maximise the potential benefit. In this context, animal experiments are still needed to optimize safety and support new modalities in diagnosis and therapy since they represent the multifaceted interactions of different complex systems and tissues.	
45	We welcome the opportunity to comment on the revision, and note the revised Guidelines provide greater clarity on several areas.	General agreement.
45	For organisations planning and overseeing early phase trials in 'patients' (as in our organisation where all trials involve patients with cancer), the references in the document which acknowledge where requirements in this setting are likely to differ are very helpful. We would suggest that more such references could be included.	General agreement.
45	Guidelines for FIH involving advanced therapy IMPs (noted to be out of the scope of the current document) would be welcomed.	General agreement.
47	Member companies conducting clinical trials have traditionally placed volunteer and patient safety at the forefront in our drug development programs. We look at what internal practices, procedures and/or processes can be adjusted to improve patient safety, especially in light of tragedies like what happened last year in France. Therefore, we welcome this opportunity to comment on this draft Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. **As might be expected, interest in this important guideline was high among member companies. Comments were obtained from 22 companies and totaled 253 pages prior to consolidation.** Generally, there was consensus that the member companies did not believe that there is a "one size fits all" application that can be specified in an algorithmic fashion to First in Human (FIH) studies. By this we strongly believe	Partly agreed. Text amended in line with these and other related comments.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	that a risk-based approach should be considered when determining the additional safe guards to first human doses. There are situations where a slow progression of dose escalation, application of sentinel dosing, capping a maximal dose, to name a few, may indeed be necessary to safeguard subjects (discussed below). There are many other situations where these approaches would be unnecessary, stifle drug development, provide a false sense of security and not well serve patients or volunteers. We believe that a risk-based approach is fundamental and any proposed guidance change should be science and evidence based. Our understanding of human pathophysiology and its relationship to nonclinical models continues to progress over the years, however, it is clear that human biology can differ substantially from animals; thus human reactions to an investigational candidate are not entirely predictable—either at the population level or at the individual level. Though various safeguards and trial design strategies are routinely implemented to mitigate this uncertainty, phase I studies are never completely devoid of risk to study participants. Investigational new molecules exist along a continuum of risk, and although the aim of Industry is to reduce this risk as much as possible, risk is never zero. While we understand the desire to eschew the artificial dichotomy of high versus low risk compounds, we believe that it is critically important to continue to utilize risk assessment as a continuum to appropriately design in FIH studies. We agree with the idea that safety is to 'take precedence over any practical, economic or regulatory considerations.' This sounds perfectly rational on its face, but there is a receiver operating characteristic (ROC) component at play here. That is, to try to decrease risk to zero is impossible and not appropriate, given that it would result in substantially increasing false positive rates (see, for example, the Sentinel Dose discussion, below). Phase I study design should be science-driven, thoughtful, rational, and tailored to the specific target biology and clinical scenario. The specific mechanism of action and target biology of any new therapeutic need to be considered in light of the study design requirements. In addition, other important factors should be considered when designing a phase I study: the nature of the novel therapeutic being tested, the potential for off-target effects, the translatability of nonclinical models (for pharmacology, pharmacokinetics, and toxicity), and operational feasibility. Furthermore, Sponsors should be able to incorporate emerging nonclinical and clinical data into the study design with relative ease	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	and agility even as it is ongoing. Vaccines Europe agrees on the need for an update on this guideline on strategies to identify and mitigate risks in First in Human studies, since general risk mitigation practices in vaccine First in Human studies are aligned with the principles of this guideline. However the proposed draft guideline has a strong focus on studies to be conducted with pharmaceutical products and does not address many specificities for vaccines trials. It should be reminded that the mode of action of vaccines is significantly different from pharmaceutical products in general and hence the design of clinical studies for vaccines is quite specific. The strategies described in the present document miss or partially address specific vaccine strategies. As examples; PK and PD does not apply to single or limited number of vaccinations or to the evaluation of the action of a vaccine. Dose escalation, the concepts and path of SAD and MAD are usually not suitable for vaccine trials. Concepts like NOAEL are not applicable or should be clearly defined in vaccine trials where local and general reactogenicity is expected. Assessment of the effect in vaccine trials is usually related to measurement of different immunological parameters at “long” post vaccination timepoints (one week, 15 days, 30 days) and not to PK and PD. measurements. Stopping rules as described in the document can be misleading for vaccine trials. The document should clarify if vaccines are or are not in scope (see comment on page 20: regarding line 114). In case they are in scope they should be modified to include vaccine specificities or a statement should be added to provide sufficient flexibility for vaccine risk mitigation approaches. To appropriately design the FIH trial to test relevant hypotheses, one must establish the risk along a continuum using a totality of evidence approach. This risk should then be used to guide the appropriate design, including sentinel dosing, measurement of PK between dose groups, dose escalation interval, and maximum dose, among other design components. **Companies were asked to submit a listing of their top 5 concerns contained in the draft guideline. Based on the received responses the following major topics of concern were identified. These are not presented in order of importance, but more or less in chronological order of occurrence in the revised draft guideline. All these topics are considered major issues, though.**	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
47	TOPIC #1 *General* Starting with the scope and subsequent sections, the revised guideline would be served by a more structured and concise wording. This should amongst others address the following issues: **1.** The current draft document suggests at various locations in the text guidance which, if not placed into the proper context, may lead to misinterpretation and opposing recommendations as compared to various ICH guidelines (e.g. ICH M3, ICH S6 and ICH E14, see also specific topics below) **2.** The document seems to overemphasize some preclinical aspects over others; therefore leading to the impression that these are prerequisites for adequate translation, while in reality the totality evidence needs to be assessed.	Partly agreed. Text amended in line with these and other related comments.
47	TOPIC #2 *This comment refers to Lines 317 – 332 Toxicology* The guidance places a great deal of the justification of toxicology animal species relevance for small molecules on the intended target similarity to humans. While this is a fair concept, 1) it is out of alignment with ICH M3(R2) requirements for a rodent and non-rodent species. And 2) it diverts the focus to primary pharmacology at the expense of off-target surveillance. This latter point is particularly important because even when a sponsor conducts an extensive in vitro off-target battery, there still could be some significant off-target protein that mediates toxicity that may be best detected in vivo. Determination of the mechanism of toxicity of target organs found in toxicity studies can be a lengthy process and may often be inconclusive. Further, determining the definitive cause of death in preclinical toxicity studies is not always possible, even when targeted studies for this purpose are conducted. Investigative studies for cause of death, mechanism of toxicity or obtaining a clinical biomarker to warn of a possible serious or life-threatening toxicity should be performed when the toxicity or mortality is of clinical relevance. Relevance would be determined by: 1) there is a modest or low exposure margin from the proposed clinical exposure range and the animal exposures where the serious toxicity or mortality is observed; 2) the sponsor is asserting that the animal toxicity is irrelevant to humans and	Partly agreed. Text amended in line with these and other related comments.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	wishes to dose humans to similar exposures – therefore studies showing that the mechanism of toxicity is animal specific would be warranted. However, when a serious or life-threatening toxicity is observed at very high doses/exposures in animal studies that far exceed the clinical range, then such follow up studies for cause of death or mechanism of toxicity are not necessary. **Proposed changes:** the following language should be added to the guidance in section 6.5 after line 319: **"For small molecule entities directed to a human target, at least one species (rodent or non-rodent) should be pharmacologically relevant, where both the availability of the target and the relative potency of the molecule against the target in the species used for toxicity studies and the intended patient population should be considered. Both species should be relevant with respect to adequate exposure and metabolism to assess the chemical toxicity. Metabolism similarity to humans can be covered by one of the 2 species or by both profiles when combined, but each species alone need not recapitulate human."** This wording is also consistent with ICH M3(R2). **Proposed changes:** the following language should replace lines 329-332 in the guidance in section 6.5 that begins with "If mortalities and/or serious…: **"When serious toxicity or mortality is observed non-clinically, these effects may require follow up studies to determine cause of death or the mechanism of toxicity if this information is relevant to the clinical trial design or safety monitoring plan. This is usually driven by the exposures where the serious toxicity/mortality is observed. If these occur at exposures in far excess of the clinical range then cause of death or mechanism of action studies would not be required. Some mortalities/serious toxicities are poorly translated to humans, for example species-specific immune reactions with mAbs. These toxicities may be categorized as not clinically relevant with the appropriate data and/or rationale.**	
47	TOPIC #3 *This comment refers to Lines 346-348 and other referrals to 'substantial amendment.'* **Requirement for a 'substantial amendment' during FIH studies**	Partly agreed. Text amended in line with these and other related

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	The guidance that “substantial amendment(s) can be used, if required, to adjust the predefined dosing selection” is not scientifically justified. PK, dose-response, and dose-toxicity relationships are often difficult to estimate from nonclinical studies, and certainly from in vitro studies. Therefore, dose escalation relationships cannot be precisely predicted. FIH is in the ”learning” phase of drug development, the protocol doses are not selected to a priori satisfy a predefined dose-exposure-response relationship. Therefore, other than the starting and maximum dose justification, requiring justification of exposure for the in-between dose level are not useful. Some aspects in lines 346 and in 389 (intentionally or not) may restrict adaptive designs in the SAD part of a FIH. Protocols should be flexibly-written which define “maximum” dose escalation steps with flexibility to use prudence in smaller dose escalation steps, depending on emerging data. Such guidance is provided on Lines 421-423. Such flexibility will avoid unnecessary ‘substantial amendment’ generation and review. Suggest only require exposure for the starting, maximum and any critical dose level of therapeutic relevance, if known. Entry into human protocols should always specify a top exposure to be tested based on the totality of evidence approach. A substantial protocol amendment would then be needed to explore higher exposures than specified in the initial protocol. The guidance should permit flexibility in provisions for dose escalation so that a pre-specified departure from the planned nominal doses (within the range of starting dose and maximum permitted dose or exposure) is not a substantial amendment. As worded presently this is not consistent with provisions in section 8.25. Aligning text with section 8.2.5 will assure that intermediate or alternative dose levels can be easily substituted in response to emerging data in order to optimally characterize PK and PD (within pre specified dose selection criteria). Furthermore, in 400-402 allows for adjusting planned dose levels without a substantial amendment. **Proposed change: “substantial amendment~~(s)~~ is not needed if the adjustments in predefined dose selection are clearly discussed in the protocol and within the ~~can be used, if required, to adjust~~ predefined dose~~ing selection~~ escalation steps in response to emerging data”.** This proposed change then aligns with text in line #400-402.	comments.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
47	TOPIC #4 *This comment refers to lines 405-433 – Maximum dose and dose range* At the stage of entry into human, the expected human therapeutic dose is hypothetical, i.e., the expected therapeutic exposures are only projections and frequently need to be revised in the course of clinical development. Therefore, there is a risk of limiting dose-escalation in the absence of dose-limiting toxicity. Provided that toxicities are monitorable, reversible, and clinically manageable and thereby in alignment with ICH M3(R2), there are multiple reasons for exploring high exposures, i.e., above the NOAEL. 1) High exposures may be required to detect efficacy: although nonclinical efficacy models and other predictive models (e.g., PKPD models) provide an estimate of the expected therapeutic dose, the true clinically efficacious dose is not determined until later in development. 2) In some therapeutic areas, patients may intentionally or unintentionally take doses that exceed their prescribed dose in the post-marketing setting (e.g., pain); thus, exploring exposures that might exceed the predicted therapeutic dose can support continued development and effective safety monitoring in future studies. 3) Phase I units offer the opportunity for unique or intensive monitoring capabilities that other settings cannot, and Sponsors should capitalize on this opportunity. The recommendation to limit testing above the NOAEL could have the unintended effect of simply shifting risk to more vulnerable populations or less well-monitored patients, which could lead to an even greater public health risk. 4) Once a drug enters late stage development or the post-approval setting, patients with altered metabolism or clearance (e.g., due to renal, hepatic, or other disease) may be unintentionally exposed to high levels; by understanding drug effects at these higher exposures, the safety monitoring plan can be better informed and can reduce potential harm. Careful exploration of potentially supra-therapeutic doses in healthy volunteers (who have greater physiologic reserve) is essential in order get adequate coverage in a less vulnerable population, and in a carefully monitored and controlled setting, to account for potential PK or PD variability	Partly agreed. Text amended in line with these and other related comments.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	that may occur later in development or in the marketed population post-approval, where the number of people exposed may be greater and the monitoring less stringent, or to account for overdoses or extra-dosing, or to explore the steepness of the dose response curve. 5) Collecting safety data at exposures above the therapeutic level enables the collection of QTc data at supratherapeutic doses (as required by ICH E-14 which states: “An adequate drug development programme should ensure that the dose-response and generally the concentration-response relationship for QT/QTc prolongation have been characterized, including exploration of concentrations that are higher than those achieved following the anticipated therapeutic doses.”). Ultimately, understanding the effects of supratherapeutic exposures can help derisk a compound and protect patients. Furthermore, this requirement is likely to have major impacts on feasibility of early phase studies conducted in the EU. In combination with the requirement to submit a major protocol amendment in order to explore exposures higher than the upper limit of the predicted therapeutic range, irrespective of clinical data collected previously and irrespective of target biology and predicted toxicities, imposes undue burdens and is not scientifically driven. We would suggest re-wording to explain that doses above the expected human therapeutic dose (if known) may need to be studied in healthy volunteers in a carefully controlled and well-monitored fashion, but at a reasonable multiple of the expected therapeutic exposure justified to provide adequate coverage for PK or PD variability in the population or meet other regulatory expectations (e.g., TQT) unless scientifically justified. Of course the usual stopping criteria would need to be justified and the intent should not be to define MTD. Specific examples that would be considered “scientifically justified” would be very helpful. Entry into human protocols should specific a top exposure to be tested; however, this should not always correspond to the expected therapeutic exposure for the reasons above. A substantial protocol amendment would then be needed to explore higher exposures than specified in the initial protocol. **MTD in healthy volunteer trials -** “A trial design using a MTD approach is considered to be unethical for healthy	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	volunteers." There are at least two potential problems with this statement: 1) The term "MTD approach" is vague and open to multiple interpretations. Some might interpret this to mean that no further escalation could occur after a cohort with any AEs or tolerability issues, no matter how minor. The term "MTD approach" should be defined or restated to clarify what is meant by such an approach. Certainly, we do not condone blindly increasing dose until lack of tolerability is encountered. The modern approach is to attempt to characterize the safety of a compound via careful dose exploration, which should include, where possible, doses well above the targeted efficacious dose. As we have discussed above, Phase 1 is the best opportunity to explore effects of supratherapeutic exposures in a controlled environment that may be used subsequently to predict response to drug-drug interactions, special populations, and overdose situations. 2) Healthy volunteers are not the only group for whom an "MTD approach" could be considered unethical. In most cases, even *patient populations* enrolled in Ph1 trials would not be treated for sufficient durations, or at sufficient exposures, to derive benefit. Hence why would they be treated differently than healthy volunteers with respect to the approach? It is important that throughout the document HV and patients are afforded the same protections and should be treated equivalently in most cases. Scientific, totality of evidence approach would include determination of how MTD is defined, e.g. increases in liver enzymes excluding liver histopathology, could define an MTD. However, this could also be a pharmacological effect and liver enzymes can be readily monitored in the clinic. This could lead to, for example, liver enzymes increasing which could be seen as exceeding the MTD. MTD may be determined also by non-severe symptoms such as e.g. nausea, fatigue, or sleep disturbances that do not constitute un-ethical exposure. To this point, the sentence starting on line 429 should safeguard subjects (patients or HV). A further example would be a trial in which healthy volunteers are dosed with increasing doses of an incretins class molecule (GLP-1) until nausea is found. This represents a well characterized, monitorable, reversible, toxicology based finding that could be interpreted as an 'MTD approach.'	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	Proposed language: **"Determination of maximum dose for phase 1 studies should be based on the overall risk assessment of the compound (e.g. steepness of the dose / exposure response curve, specific risks related to the MoA or off-target effects etc.), the toxicology findings, and its available nonclinical and clinical PK/PD data.** **When supported by toxicology studies and clinical safety monitoring, maximum dose may exceed NOAEL, and doses that achieve near maximum PD effects** **Excessive exposure multiples beyond maximum PD effects should be avoided, unless justified by scientific necessity and adequate safety monitoring plan.** **In some circumstances, based on the totality of evidence of risk for healthy subjects, the achievement of a MTD may be a reasonable objective in this population."**	
47	TOPIC #5 *This comment refers to section 8.2.6, lines 575-578* **Scientific basis for sentinel dosing** A blanket requirement for sentinel or staggered dosing in every cohort at every dose level with a standardized design across all cohorts in all studies may be unnecessary, unscientific, and ultimately unhelpful. Sentinel and staggered dosing strategies should be scientific, risk-based, and tailored to the specific situation. Points to consider when devising the specific design of a sentinel cohort or staggered dosing strategy include biostatistical factors (expected frequency of SAEs and the sample size), the pharmacologic relevance of a given exposure (e.g., receptor occupancy), inter-individual variability (e.g., baseline characteristics, exposure differences, metabolism differences, variability in the PD effect), the PK/PD relationship, the target biology, the potential for hysteresis, and the potential for off-target effects. The vast majority of the time, the practice of conducting a sentinel dose will reveal no significant safety findings or adverse events (no serious adverse events [SAEs]). Without the rest of the cohort (or other cohorts) or placebo to	Partly agreed. Text amended in line with these and other related comments.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	compare to, there is limited information to interpret the significance of the adverse event (whether it is drug related). Potentially, if the conservative approach is taken, a number of drugs may be inappropriately terminated in Phase 1 due to random AEs in single sentinel doses that are not drug related. On the other hand, if only serious adverse events are flagged, the problem of a low positive predictive value only worsens. Given that sensitivity should be high (low false negative rate so we don't miss dangerous drugs), the specificity must decrease given the nature of most tests and the ROC model. Further, if the prevalence (prior probability) of a drug in non-oncology Phase 1 clinical trials causing an SAE is low (<1%) the positive predictive value [PPV] (True positives [TP]/TP + false positives [FP]) of the test becomes drastically reduced. If the PPV is very low, either drugs are killed inappropriately, or there becomes the issue of 'crying wolf', when a positive signal is not believed, as it is more likely to be a false positive than a true positive. Therefore, utilization of where a compound lies on a continuum of risk is critically important in the design of a trial. The likelihood of a sample size of 1 yielding data which is interpretable needs to be assessed prior to instituting a sentinel dose. If the drug has a reasonable potential in stimulating a large safety signal versus noise, a sentinel dose may be helpful. For example in case of unpredictable translation to human in combination with clear safety risks from toxicology data/ or on target PD. This is unlikely to be common. **Proposed change:** ~~It is considered appropriate to design the administration of the first dose in any cohort so that a single subject receives a single dose of the active IMP. When the study design includes the use of placebo it would be appropriate to allow for one subject on active and one on placebo to be dosed simultaneously prior to dosing the remaining subjects in the cohort.~~ **"Sentinel dosing, where a single subject receives a single dose of the active investigational medicinal product (IMP) prior to the rest of the cohort, should be considered for inclusion predicated on a risk-based, totality of evidence approach. Sentinel dosing should be applied to SAD and MAD trial designs where the prior probability of risk is large enough that a dose may be associated with an SAE, so as that the positive predictive value of the single subject/patient will be likely to yield a true positive result. Accordantly, a lower risk compound would be best served by data from a full cohort before decisions are**	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	made on dose escalation. This risk is dependent on the NME mechanism of action, potential target, cascade activation potential, toxicology, etc. (see section of risk continuum).”	
47	TOPIC #6 *This comment refers to lines 683-688 and lines 595-606* **PK-based (individual vs. mean) dose decisions, and requirements for dose escalation in general** Using the non-clinical exposure (C_{max} or AUC) at the NOAEL to set dose stopping criteria may be too restrictive as discussed under topic 4. This issue, regardless whether or not the NOAEL is used as a stopping criterion, would be further exacerbated by limitations due to measurement and outlier (individual) PK assessment, rather than use of the mean for dosing decision making. There is certainly limited scientific rationale for comparing an extreme exposure in one individual in a cohort (i.e., an outlier value) to a safety margin derived from an average exposure value in the toxicology species. The therapeutic exposures in humans are typically not known for novel mechanisms, and cannot readily be predicted form non-clinical models. Therefore, exploration of safety in early phase studies (in preparation for later phase studies) should be allowed beyond non-clinical NOAELs when nonclinical toxicities beyond the NOAEL are considered monitorable, manageable, and reversible. Also, there is a risk that the PK dose stopping criteria could become unnecessary restrictive in cases: 1) Where NOAELs derived from the most sensitive species is based on an observed toxicity or exaggerated pharmacology, which can be scientifically justified as being irrelevant to the trial subjects or can be monitored in the FIH/early CT by an appropriate biomarker (e.g. weight loss of obesity compound). 2) Where NOAELs from longer repeated dose studies (13-, 26-, 39- week) are used for setting stopping criteria in SAD CTs. A totality of evidence approach to risk and subsequent monitoring in the FIH trials, taking all available data into consideration during the trial, is the most scientifically justified approach to dose escalation.	Partly agreed. Text amended in line with these and other related comments.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	1. Safety data should be the primary driver to determine dose-escalation: a. There are many examples in which human are the most sensitive species for a given toxicity (including the French case), in which SAEs occurred within the NOAEL exposure range. b. There are also cases in which humans tolerate certain toxicity better than toxicity species, as a result, clinically beneficial doses has MOS < 1 (i.e. NSAIDS). c. PK should not be used as a surrogate for safety monitoring. 2. PK (exposure) data should be used to support phase 1 trials: a. In cases when the toxicity findings are not monitorable, irreversible and potentially life-threatening: in such cases, PK may be used for dose selection to safe guide safety of phase 1 subjects b. PK data can be used as supportive information for dose-escalation in most of cases in which tox findings are monitorable, reversible and non-life threatening. i. PK data from lower 2-3 doses can be used to predict the exposures at higher doses ii. Review of PK data may reveal supra-proportional exposure, in which cases increments of dose escalation should be decreased. 3. PD data, when available, may also aid the dose-escalation in phase 1 trials: a. Steep dose-response relationship may alert sponsors to reduce the increment of dose escalation, especially, the PD effect is of narrow therapeutic margin b. Increment of dose escalation may also decrease when E_{max} is approaching. Consequently we propose the following changes:	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	Line 597-598: Proposed change: Thus all relevant data to the stopping criteria and to specific risks of concern from cohort "n" should be reviewed prior to allowing dosing of cohort "n+1". **Lines 602-605: Proposed change:** All emerging PD, PK and safety data relevant to the stopping criteria and to specific risks of concern should be critically reviewed against the pre-defined stopping criteria (see section 8.2.10), including exposure limits that are not to be exceeded(….) While there can be no delay for safety data, a lack of PD information or a reduced PK data set could be justifiable in some cases, such as a short duration of the PD effect, and in cases these data are not relevant to the stopping criteria and to specific risks of concern. **Lines 683-688: Proposed change:** Deletion of the following~~: "Comparisons of the non-clinical and clinical exposure should be based on the maximum clinical exposure in an individual subject within a cohort and not mean (average) clinical exposure in a cohort."~~ Suggest changing sentence to **"If severe toxicity or death are observed in a nonclinical species without premonitory signals, and no appropriate clinical biomarker is available, a dose stopping criterion should be included at the clinical exposure (Cmax or AUC) equivalent to the exposure achieved at the NOAEL determined in the most relevant non-clinical species in a study of relevant duration compared to the duration of the clinical trial. The NOAEL in this extreme case should be adjusted by safety factors if appropriate and based on available PK data. Exploration of exposures beyond non-clinical NOAEL levels are justifiable if 1) toxicities are considered monitorable, manageable, and reversible - and 2) doses have scientific and medical justification "**	
47	In several places, reference is made to "Maximum exposure": for certain drugs (highly protein bound drugs, on a case-	Not agreed. Term 'maximum exposure'

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	by-case basis), it could be more relevant to use free drug exposure as guidance.	preferred.
47	The changes proposed in this guidance go significantly beyond the scope of current ICH guidelines. They deviate from the existing ICH guidance (especially for the non-clinical part) and add expectations that exceed current ICH guidance.	Not agreed. It is stated the guideline should be read in conjunction with Directive 2001/83/EC and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations. Consistency with ICH was considered in detail.
47	The guidance is overly prescriptive in the scientific principles required in a regulatory submission, which may lead to the unnecessary use of animals and slow clinical development and, importantly, access of beneficial medications to patients.	The revision is intended to further assist stakeholders in the transition from non-clinical to early clinical development and in identifying factors influencing risk for new IMPs.
48	Regeneron welcomes the initiative by the Agency in revising this 'Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products'. In particular the incorporation of early clinical trials beyond those strictly defined as first-in-human in the guideline is welcomed. As a general comment we would note that there may be some areas of the proposed guidance that may not strictly apply in the development of biologic products. These areas are noted in the specific comments which follow.	General agreement.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
49	1. The Royal Statistical Society (RSS) is a learned society and professional body for statisticians and data analysts, which promotes statistics for the public good. Our strategy supports strengthening both the profession and the discipline of statistics, and medical and pharmaceutical trials clearly set an example and a high standard for this, as statistics play a crucial part in reducing the risk of harm. Our commentary which follows focuses on statistical issues for your draft Guideline, and refers to recommendations made by the Royal Statistical Society's (RSS) Working Party on Statistical Issues in First-in-Man Studies[1]. We comment on those aspects that relate strongly to RSS's recommendations, as follows: 2. In the BIAL/Biotrial clinical trial[2], one problem was that the pre-specified decision criteria, as approved by ANSM, were per-cohort, not across-cohorts as the EMA Guidance rightly requires (see Bird et al., 2017[3]). It is important to note where and how this would be addressed by implementing the new draft guidance: 2.1. A clear statement is made at lines 345-346 that: "The starting dose and estimated exposure levels chosen for all cohorts and study parts should be pre-specified and a justification for these steps should be outlined in the study protocol". 2.2. Section 8.2.6 (lines 575-593) of the EMA Guidance should also highlight more precautionary designs, because serious adverse events may not manifest themselves in all participants at the same speed. For example, in Cohort 5 of the Multiple Ascending Dose phase of the BIAL/Biotrial clinical trial, only a third of actively treated subjects became ill on the fifth day of exposure, while others became ill later. In Section 8.2.6, the EMA Guidance appears to suggest that a single sentinel pair (active; placebo) per cohort is sufficiently precautionary. Please see RSS recommendations to the contrary[4] and note that line 575 "in any cohort" should probably read "in every cohort" to convey more accurately the suggestion that the EMA Guidance makes. 2.3. The draft guidance (sections 7.1-7.4, lines 351-353) stipulates that the methods used and calculations on how doses and estimated exposure levels were determined, including methods for modelling, should be included in the Investigator's Brochure, and summarised in the protocol. We particularly value the requirement for summarisation in the protocol. This is essential to meet RSS 'open protocol' recommendations, since the Investigator's Brochure is not	Partly agreed. Text amended in line with these and other related comments.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	generally in the public domain. Welcome also, in the RSS spirit of 'open protocol', is the requirement (at line 382) that: "Any safety factors used should be justified and detailed in the Investigator's Brochure and protocol". This needs to fulfil RSS's recommendation[5] that "Before proceeding to a first-in-man study, there should be: • Quantitative justification of the starting dose - based on suitable preclinical studies and relevant calculations. • A priori assessment of the risk level for the recommended study dose(s). • Appraisal of the uncertainty about these recommendations." 2.4. In the BIAL/Biotrial clinical trial, the desired effect of the drug in humans was observed at much lower doses than anticipated. The EMA Guidelines should give a clear recommendation to reconsider the planned dose-escalation in such cases. 3. We suggest wording needs to be strengthened in section 4.4 and section 6 (lines 235-236) where "the inclusion of a tabulated summary containing an overview of all relevant non-clinical data is encouraged". The findings of non-clinical safety studies that are relevant when designing first-in-human and early clinical trials need to be considered. The EMA's Guidance should explicitly set out that these findings are summarised quantitatively in the protocol. In particular, all animal deaths in the pre-clinical studies should be reported in the protocol (at lines 207-208, 235-236, 280-281 and 329-332). We welcome the principle at lines 280-281 that "A weight-of-evidence approach should involve integration of information from in vivo, ex vivo and in vitro studies into the decision-making process." 4. We particularly value the requirement (line 91) for protocols to nominate and justify a pre-defined maximum dose. The EMA Guidance reiterates (at lines 409-411) that: "A maximum dose or exposure, which should not be exceeded in the study without approval of a substantial amendment, should be pre-defined and justified in the protocol for the full clinical trial and/or each study part." 5. We welcome the clear assertion (at lines 432-433) that: "A trial design using a maximum tolerated dose approach is considered to be unethical for healthy volunteers".	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	6. In respect of dose escalation, the EMA Guidance rightly highlights non-linear pharmacokinetics (PK), and the reliability with which potential adverse effects can be monitored in humans before they escalate into something serious or irreversible (lines 396-399). In moving from single to multiple dosing, the EMA Guidance correctly requires (lines 438-439) that: “particular attention should be paid to linear versus non-linear PK in the expected concentration range, the PK half-life versus duration of action and the potential for accumulation.” 7. The EMA Guidance is correct (at lines 590-593) that more precautionary cohort-designs could be needed at later stages, e.g. on the steep part of dose-response curve or when approaching target saturation levels or exposure margins. Conversely (at lines 617-618), since the initial doses may be very low, early cohorts may not show any pharmacological effects. 8. The EMA Guidance suggests, but does not insist in Section 8.2.8 on Precautions to apply between study parts, that: “For studies with multiple parts, consideration may be given to submitting an interim report to the competent authorities for review as a substantial amendment prior to the start of further dosing phases” (see lines 634-636). It is not clear whether it is the sponsor or the authorities who are making the substantial amendment. If interim reports are desirable we suggest that it should be clearly stated (a) that they are mandatory, and (b) precisely between which study parts they are needed, and (c) whether the later study parts need to wait on further approval. 9. In the draft guidelines’ Executive Summary (lines 71-74), strategies for mitigating and managing risks do not explicitly mention study design separately from the conduct of the clinical trial. In the last twenty years some designs have been proposed which maintain the rule that each cohort corresponds to a dose increment but have more flexibility in the number of subjects on placebo, or even on lower doses, within that cohort[6]. It has been shown that these new designs have several advantages. (1) more information about the effects of the different doses is obtained from the same number of subjects, because there is less confounding of differences between doses with differences between cohorts. (2) They are safer, because the number of subjects given each new dose in the same cohort is smaller.	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	(3) Because it is no longer the case that most subjects in each cohort receive the same dose, blinding is much more effective. On the other hand, there are still issues to discuss about such designs, including the following. (A) If each dose is given to subjects in a number of cohorts, how and when can pharmacokinetic / pharmacodynamic studies be done on that dose to inform the choice of next dose? (B) If we are trying to find a safe dose to give to people, is it more important to compare it with the control or to compare it with the next lowest dose? We believe the EMA guidelines ought to discuss such designs, and encourage investigation into finding better designs for first-in-human trials. [1] Senn, S. Amin, R. Bailey, A. Bird, S.M., Bogacka, B. Colman, P. Garrett, A. Grieve, A. & Lachmann, P. (2007) 'Statistical issues in first-in-man studies', *Journal of the Royal Statistical Society, Series A* 170: 517–579, or the RSS Report (PDF) available at: http://www.rss.org.uk/Images/PDF/publications/rss-reports-statistical-issues-first-in-man-studies-2007.pdf [2] Fassbender, M. (2016) ''Clear statistical reservations' surround Bial's fatal clinical trial', *in-Pharma*, 2 February 2016. Available at: http://www.in-pharmatechnologist.com/Regulatory-Safety/Clear-statistical-reservations-surround-Bial-s-fatal-clinical-trial [3] Bird, S.M. Bailey, R.A., Grieve, A.P. & Senn, S. (2017) 'Statistical issues in first-in-human studies on BIA 10-2474: Neglected comparison of protocol against practice', *Pharmaceutical Statistics* 00:1–7. Available at: https://doi.org/10.1002/pst.180 [4] Recommendations no. 9 and 10 in Senn *et al*. (2007) say: "Unless arguments have been provided that the risk is so low that simultaneous treatments are acceptable […] a proper, or sufficient, inter-administration interval needs to be proposed and observed", and "First-in-man study protocols should provide justification of the proper interval between administration to successive subjects." Additionally, Bird *et al* (2017) conclude that in some or all cohorts, multiple sentinel-pairs may be necessary, and that regulators should specifically assess how well safeguarding is justified per-cohort. [5] Recommendation 4 in RSS (2007) 'Statistical issues in first-in-man studies', available at: http://www.rss.org.uk/Images/PDF/publications/rss-reports-statistical-issues-first-in-man-studies-2007.pdf [6] Some of these are described briefly in (a) Senn, S. *et al.* [ibid] (2007) 'Statistical issues in first-in-man studies', available at: http://www.rss.org.uk/Images/PDF/publications/rss-reports-statistical-issues-first-in-man-studies-2007.pdf There are more details in	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	(b) Senn, S. (1997) *Statistical Issues in Drug Development*. Wiley: Chichester; and (c) Bailey, R.A. (2009) Designs for dose-escalation trials with quantitative responses (with discussion). *Statistics in Medicine* 28: 3721–3760.	
50	Roche welcomes the opportunity to participate in the public consultation on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products as an important opportunity to share its views on this topic. First and foremost, Roche wants to express its support to the contribution made by the EFPIA to the consultation. In addition to our contribution to the EFPIA comments, Roche would like to highlight several specific aspects and to provide supplementary considerations. We are submitting a listing of our top 5 topics of concern contained in the draft guideline. To facilitate ease of access by the reviewer, please find below in the general comments section the discussion about these top 5 topics. <u>Intrinsic Risk of First-In-Human (FIH) Studies:</u> Although the use of non-clinical models plays a critical role characterizing the potential risks and benefits to humans, the translatability of these models to humans must be interpreted cautiously. Thus effects in humans of an investigational medical product are not entirely predictable from the non-clinical models—either at the population level or at the individual level. Though various safeguards and trial design strategies are routinely implemented to mitigate this uncertainty, FIH studies are never completely devoid of risk to study participants. Investigational medical products exist along a continuum of risk, and this risk is never zero. In order to account for these uncertainties, FIH study design should be science-driven, thoughtful, rational, and tailored to the specific target biology and clinical scenario of the agent under investigation and the intended patient population. In addition, other important factors should be considered when designing a first-in-human study: the potential for off-target effects, the translatability of nonclinical models (for pharmacology, pharmacokinetics, and toxicity), and operational feasibility. Furthermore, sponsors should be able to incorporate emerging nonclinical and clinical data into the study design with relative ease and agility even as it is ongoing. Importantly, FIH healthy volunteer studies are typically conducted in phase I units that offer rapid accessibility to acute medical care if needed, as well as opportunities for unique or intensive monitoring—more so than subsequent studies. Sponsors should make use of this special opportunity in clinical development to fully understand drug effects at multiple dose levels, including	Partly agreed. Text amended in line with these and other related comments. The concept of an uncertainty (risk based) approach has been introduced throughout the guideline.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	levels above the predicted therapeutic dose, in order to reduce risk in subsequent studies where participants are less monitored. The guideline should outline the key aspects of the drug development that may require different considerations for: • Different therapeutic areas: oncology versus non-oncology • Different types of molecules: small molecules versus larges molecules (eg, antibodies, non-antibody protein based drugs such as cytokines, antibody-drug-conjugates,…) A “one size fits all” approach that spans all phase I studies may not account for this and hence could be inappropriate and counterproductive. FIH studies in some oncology, and seriously ill populations, are further examples where approaches may differ from the “one size fits all” approach outlined in the guidance. Human specific toxicities can never be fully de-risked or predicted from nonclinical studies; and translation from non-clinical to clinical must always be done cautiously, regardless of the number of species tested or the number of experiments performed.	
50	*This comment refers to section 8.2.6, lines 575-578* <u>Scientific basis for sentinel dosing</u> Because significant human toxicities can be difficult to predict accurately from non-clinical models, we agree that sentinel dosing and/or staggered dosing, if implemented in a thoughtful manner, can reduce risk in first-in-human studies. However, a blanket requirement (or “one size fits all” approach) for sentinel or staggered dosing in every cohort, at every dose level, with a standardized design across all studies, with all types of investigational molecular products (e.g., one subject to receive active drug as described in lines 576-577) may be unnecessary and ultimately unhelpful in reducing risk. In fact, if the sentinel is not designed with consideration of the anticipated PK or the pharmacology or the pattern of safety issues of concern, it is quite possible to be falsely reassured by a “clean” single sentinel subject after a defined period of observation, especially if exposures will continue to increase after an observation period (i.e., if the sentinel observation period ends before steady-state is achieved) or if serious adverse events do not occur in all exposed subjects in the same manner (i.e., if some subjects have a delayed response or less severe adverse events). In addition, the strategic determination to apply a sentinel approach must take into	Partly agreed. Text amended in line with these and other related comments on sentinel dosing.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	consideration the various kinds of investigational medical products (small molecules, antibodies, antibody-drug-conjugates, cytokines, etc.). Therefore, sentinel and staggered dosing strategies should be scientific, risk-based, and tailored to the specific situation. One potential problem with sentinel dosing and the possibility of false reassurance is illustrated with the following. The concept of Number Needed to Harm, i.e., NNH = 1/(prob_exposure-prob_nonexposure) = 1/ (absolute risk increase above background) tells us that a sentinel group of one on active and one on placebo can only detect AEs with a high probability of occurrence. For example, if the true frequency of SAEs is 100% in exposed subjects, as with TGN1412, then a sentinel group of one will be effective since the NNH=1. However, if the true frequency of SAEs is 50%, which is still unacceptably high, then the NNH would be 2, i.e., on average, two or more subjects would need to be dosed for one to have an SAE. In such a case, a “clean” sentinel could be falsely reassuring. Bayesian adaptive designs represent a supplementary approach to sentinel dosing that can further reduce the chance of dosing individuals at a non-tolerated dose. Dose-escalation increments are based on the prediction of the percentage of dose-limiting adverse events expected at the next dose level, based on accumulated experience. Bayesian adaptive designs show a good performance in the estimation of MTD and in reducing the total number of HVs exposed. Some points to consider when devising the specific design of a sentinel cohort or staggered dosing strategy should include variables that could significantly affect the likelihood of the sentinel cohort of detecting toxicity. These include: • Biostatistical factors (i.e., the expected frequency of SAEs and the sample size, since low frequency events will be unlikely to occur in one sentinel subject • The pharmacologic relevance of a given exposure (e.g., receptor occupancy), since a low receptor occupancy state will have a lower probability of a drug-related adverse event than a high receptor occupancy state • Inter-individual variability (e.g., baseline characteristics, exposure differences, metabolism differences, variability in the PD effect), since adverse events can present differently in different individuals • The PK/PD relationship	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	• The target biology • The potential for hysteresis of serious toxicities • The potential for off-target effects. Proposed change: ~~"It is considered appropriate to design the administration of the first dose in any cohort so that a single subject receives a single dose of the active IMP. When the study design includes the use of placebo it would be appropriate to allow for one subject on active and one on placebo to be dosed simultaneously prior to dosing the remaining subjects in the cohort.~~ ***Sentinel or staggered dosing is a risk-mitigation strategy that should be considered in certain situations, both in single and multiple dose studies, in order to reduce the risks associated with exposing all subjects in a cohort simultaneously. The protocol should justify when and how sentinel dosing is to be used and should also describe the scientific rationale for the specific design of the sentinel strategy. Sentinel dosing may be appropriate at all doses or only at the doses where the risk of significant toxicities may be increased, such as the first dose administered to healthy volunteers or the first dose administered to a population that may be particularly vulnerable to certain toxicities. Other scenarios may also lead to implementation of sentinel or staggered dosing: when receptor occupancy is expected to be high, when off-target effects might be more likely, when doses are considerably higher than the expected therapeutic dose, when a pattern of clinical findings emerges and is divergent from nonclinical toxicology results, when the safety margin (e.g., calculated from the NOAELs in nonclinical studies) is narrow, or when one or more subjects has experienced a safety or tolerability issue that would be unacceptable if it occurred more frequently or more severely in subsequent cohorts. If sentinel dosing is not planned for one or more cohorts, justification should be provided in the protocol. Furthermore, Sponsors should realize that sentinel dosing can reduce risk but will not eliminate risk to subsequent subjects.*** ***In addition to sentinel dosing, the use of Bayesian adaptive dose escalation designs should be considered where prior information and data from all dose levels are used to estimate the probability of adverse***	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	events at future doses. This is used to guide the choice of the next dose level. Cohort sizes can be small initially and increased at doses expected to be most informative such as those in the linear portion of the dose-response curve for pharmacology or those that are close to a pre-determined level of unacceptable adverse events."	
50	*This comment refers to section 8.2.10, lines 652-676* <u>Stopping Rules for healthy volunteer trials</u> We agree that the protocol should define clear and unambiguous stopping rules, and that such stopping rules serve as a protection for subjects in clinical trials. However, this recommendation, as currently written, is potentially overly stringent and does not leave room for medical judgment. The numbers of subjects with certain adverse reactions that would lead to stopping (i.e., line 676 "…two subjects in the same cohort") appear somewhat arbitrary and would seem to encourage smaller size cohorts, which would minimize the chances of meeting stopping rules and would be at odds with the goals of phase I studies which are to better understand safety, tolerability, and PK. Also, if an SAE or severe non-serious AE occurred in a placebo-treated subject, even if considered possibly related by a blinded investigator, this should not trigger cessation of dose escalation. Thus, the text should clarify that these events need to occur in subjects who have received the active drug. Published reports on phase I studies (e.g., BMJ 2015;350:h3271) have demonstrated that the majority of SAEs in healthy subjects are not drug related. If the Investigator and Sponsor agree after reviewing the data that the SAE is clearly not related to study drug (because a clear alternative explanation exists for the SAE), then stopping should not be necessary and a substantial amendment should not be required (as specified by lines 656-658). Furthermore, with regard to "severe non-serious ARs" severity may depend on the grading scale used, and it's important to note that there is no universally accepted grading scale, particularly for healthy volunteer studies. Also, there may be "severe" AEs that are not clinically significant, and clinical significance may in part depend upon the duration of the effect. Ultimately, there should be room for medical judgment in assessing clinical significance.	Partly agreed. Text amended in line with these and other related comments on stopping rules.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	Proposed change: Lines 653-656: "The protocol should define unambiguous stopping rules which result in an immediate stop to dosing. It should further be specified in the rule if it implies a final end of dosing or a possible temporary halt ~~with dosing re-starting after a full evaluation of available data and the approval of a substantial amendment.~~ ***In general, in FIH studies, all clinically significant adverse events should be presumed to be related to study drug, particularly in healthy volunteers. However, after further review of additional clinical data, the Sponsor and Investigator may conclude that one or more adverse events are not related to the study drug because an alternative and more-likely explanation has been clearly identified. If this occurs, the rationale for this decision must be clearly documented, and dosing may be re-started.*** ~~The submitted substantial amendment should include a justification of the proposed dosing for the continuation of the trial and details of any adjustments to the protocol including additional safety monitoring, if applicable."~~ Lines 672-676: "Stopping rules for healthy volunteer trials should include: • a 'serious' adverse reaction (AR) (i.e. a serious adverse event (AE) considered at least possibly related to the IMP administration) in one subject ***who received active study drug*** • 'severe' non-serious ARs (i.e. severe non-serious AEs considered as, at least, possibly related to the IMP administration) in two subjects in the same cohort ***if the severe effects are deemed to be medically significant by the Investigator or the Sponsor and occurred in participants who received active study drug"*** In addition, please state whether these stopping rules are applicable to a cohort of a specific size. Furthermore, please clarify if the severe AEs need to be in the same system-organ-class or should together suggest a pattern of toxicity.	
50	*This comment refers to section 7.4, lines 424-425* We agree that using nonclinical models and simulations to predict the efficacious exposures is important to guide	Partly agreed. Text amended in line with these

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	dosing. Significant progress has been made in this discipline. However, we must also realize that such models are imperfect, are not equally predictive in all therapeutic areas, and may not always directly translate to humans. Thus, the predicted efficacious exposure should be used as a guide rather than as a strict limit. At the stage of entry into human, the expected human therapeutic dose is hypothetical, i.e., the expected therapeutic exposures are only projections and frequently need to be revised in the course of clinical development. The recommendation to not exceed the expected therapeutic dose range in healthy volunteers is potentially problematic. Provided that toxicities are monitorable, reversible, and clinically manageable, there are multiple reasons for carefully exploring high exposures, i.e., exposures that exceed the expected therapeutic range or even may exceed the NOAEL. First, subsequent to the FIH study, e.g., in phase II and beyond, some patients are likely to be exposed to supratherapeutic exposures for a variety of reasons: PK or PD variability, overdose (as often intentionally or unintentionally occurs with pain medications), dosing errors, impaired clearance that may occur with certain diseases, and under other circumstances. Because monitoring is less stringent in studies subsequent to the FIH study, if the clinical effects of such supratherapeutic exposures remain undefined after the FIH study, this recommendation could have the unintended consequence of simply shifting risk to more vulnerable and less well-monitored populations. This could lead to a public health risk. Careful exploration of potentially supra-therapeutic doses in healthy volunteers (who generally have greater physiologic reserve) is therefore important to support continued development and more effective safety monitoring in future studies. It also provides a means to obtain adequate coverage in a less vulnerable population. (Of note, phase I units offer the opportunity for unique or intensive monitoring capabilities that other settings cannot, and Sponsors should capitalize on this opportunity.) Second, high exposures (relative to nonclinical efficacy models) may be required to detect efficacy in the clinic. Although nonclinical efficacy models and other predictive models (e.g., PKPD models) provide an estimate of the expected therapeutic dose, the true clinically efficacious dose is not determined until later in development. Third, this recommendation directly contradicts existing ICH guidance – e.g., ICH E14 which states: “An adequate drug	and other related comments.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	development programme should ensure that the dose-response and generally the concentration-response relationship for QT/QTc prolongation have been characterized, including exploration of concentrations that are higher than those achieved following the anticipated therapeutic doses."Ultimately, understanding the effects of supratherapeutic exposures can help derisk a compound and protect patients. Importantly, each molecule must be considered on a case-by-case basis, and different limits (higher or lower) may be appropriate in different situations. Furthermore, this is likely to have major impacts on feasibility of early phase studies conducted in the EU. The requirement to submit a major protocol amendment in order to explore exposures higher than the upper limit of the predicted therapeutic range, irrespective of clinical data collected previously and irrespective of target biology and predicted or observed toxicities, imposes significant challenges. Guidance should be provided on what specific scientific justifications would enable exploration of supratherapeutic exposures in healthy volunteers. Proposed change: Lines 424-425: "~~In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified.~~ ***In general, for healthy volunteers confined to a phase I unit where intensive monitoring and quick access to on-site medical care are readily available, exposure at a reasonable multiple above the expected therapeutic dose range (i.e., the exposure range predicted by nonclinical efficacy models) may be carefully explored provided that predicted toxicities are monitorable, reversible, and clinically manageable. For such situations, scientific justification must be clearly provided in the protocol. An example of such a situation would include a small molecule that is being developed for a therapeutic area (such as a CNS indication) where overdose might be expected, where there is considerable uncertainty around the translatability of the nonclinical efficacy model(s), and/or where adequate safety margins exist above the predicted therapeutic dose range.*** ***As with all first-in-human studies, clear stopping criteria should be described, and the intent should not be to find a non-tolerated dose.*** ***Testing of higher exposures than specified in the initial protocol would require a substantial protocol***	

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	amendment with scientific justification." Other specific examples that would be considered "scientifically justified" would be very helpful.	
50	*This comment refers to section 8.2.10, lines 686-688* <u>PK-based (individual vs. mean) dose decisions</u> We recognize that basing decisions on exposure outliers (e.g., maximum rather than mean exposure) will provide an additional margin of safety, which could be appropriate when the potential toxicity is serious and when the dose-response relationship is steep. However, implementing this approach across all studies irrespective of the specific considerations will likely lead to inappropriate decisions. A blanket requirement (or "one size fits all" rule) to always use this approach is overly-stringent. Under current FIH study practice, outliers are already incorporated into dose escalation decisions, which are typically rendered based on the exposure, safety, and tolerability observed in all subjects. Strictly limiting dose escalation in all FIH studies based on outliers could lead to premature termination of dose escalation and could have the unintended consequence of preventing subsequent participants from achieving therapeutic exposures. This in turn could lead to erroneous conclusions about the activity or effectiveness of a drug. Please clarify the rationale for comparing an extreme exposure in one individual in a cohort (i.e., an outlier value) to a safety margin derived from an average exposure value in the toxicology species. Consider removing this requirement or providing clarification on the specific situations where such an approach is indicated. Proposed change: "~~Comparisons of the non-clinical and clinical exposure should be based on the maximum clinical exposure in an individual subject within a cohort and not mean (average) clinical exposure in a cohort.~~ ***In most cases, safety margins derived from nonclinical studies are based on a comparison of mean nonclinical exposures to mean clinical exposures. However, in certain circumstances in which the potential toxicity of the IMP is serious or unmonitorable and/or when the dose-response relationship is predicted to be steep, it may be appropriate to limit dose escalation based on individual rather than mean (average) exposure, i.e., when***	Partly agreed. Text amended in line with these and other related comments.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	an individual achieves a certain exposure (e.g., some fraction of the NOAEL determined in the most sensitive non-clinical species).”	
50	*This comment refers to section 6.1, lines 244-284* Increased emphasis on nonclinical models to effectively predict the target therapeutic dose range: Given the broad nature of the guidance it must be recognized that the quantitative ability of non-clinical pharmacological models varies widely across therapeutic areas and likely even across targets within therapeutic areas. Consequently the absolute quality of submissions, ability to evaluate and relative subject safety will vary similarly. When the species used for pharmacological models differ from those used in toxicology studies, the ability to define pharmacological activity and safety in the same species and thereby derive a therapeutic ratio may be challenging. There are uncertainties and unknowns about translation of non-clinical models to human disease. Proposed change: Acknowledge that although nonclinical models can provide a scientific basis for predicting the efficacious exposure range, they cannot definitively predict the therapeutic exposure. Therefore, they should be used as a tool to guide dosing rather than an absolute limit on early phase studies. Clinical experience obtained later in development will ultimately define the therapeutic range. Lines 244-246: **“**The search for a relevant animal model should be documented and the model selected should be 246 justified in the Investigator’s Brochure (IB). ***The relative strengths and limitations of the animal model(s) should be described.”*** Lines 263-265: “The use of in vitro human cell systems could 264 provide relevant additional information, especially for the translation of the mode of action from animal 265 to human. ***Sponsors are encouraged to use human tissues or human cells as a component of nonclinical safety evaluation where possible and when appropriate in order to help de-risk human specific toxicities or predict human-specific effects.”***	Partly agreed. Text amended in line with these and other related comments.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
51	The Biotechnology Innovation Organization (BIO) thanks the European Medicines Agency (EMA) for the opportunity to submit comments on the “Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products.” BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products. In general, it is important that the guideline acknowledges and differentiates the requirements for trials conducted in high-morbidity and high-mortality disease states such as advanced stage cancers, as in such settings more flexibility should be applied, and as already recognized by regulators in other guidance documents (e.g., ICH S9 guideline). Key comments included in the below include discussion of maximum doses in healthy volunteer studies (line 424); sentinel dosing (line 557-578; and no need to submit an interim report necessarily as a substantial amendment (lines 634-636). We provide further, detailed comments to the draft guideline below.	Partly agreed. Text amended in line with these and other related comments.
52	The guideline should specify more clearly what is considered an early trial. If a phase 1 safety and PK trial was completed, is the proof of concept in scope or only if part of an integrated protocol? If there is a change in formulation when there’s already patient exposure data, is that in scope? The scope description is open to interpretation and the guidance may end up being applied to trials it was not intended to.	Addressed in scope.
52	Clarify if the scope (Line 114) does or does not apply to Herbal Medicinal Products.	Addressed in scope.
54	This guideline does not take into consideration the specific properties of radiopharmaceuticals. We therefore suggest to extend the disclaimer in Chapter 2 Scope, lines 114-116 (page 5) to radiopharmaceuticals “While many of the scientific principles included in this guideline apply to advanced therapy investigational medicinal products **and radiopharmaceutical IMPs** as well, these products are not included in the scope of this guideline.” Justification: In general the guideline is written considering therapeutic, pharmacologically active pharmaceuticals, which is gouverned by different principles than diagnostic (radio)pharmaceuticals. Diagnostic radiopharmaceuticals are given in doses that do not result in any pharmacological effects (=below NOAEL and PAD), typically as a single	Addressed in scope.

Stake-holder no.	General comment (if any)	Outcome (if applicable)
	application in a very well controlled clinical environment. Half-lifes of radionuclides are very short usually in the range of hours. The radiation doses and subsequent risk assessment from diagnostic radiopharmaceuticals in early clinical trials do not differ from diagnostic radiopharmaceuticals in clinical practice. For therapeutic radiopharmaceuticals the therapeutic effect is solely based on radiation emitted by the decay of the radionuclide. These effects can be calculated in dosimetric studies and the organ most sensitive to radiation (“dose limiting organ”)sets the limit for the dose.Therefore chapter 7 (dosing selection) is not applicable to radiopharmaceuticals. Application of this guideline would create additional hurdles in the design and conduct of clinical trials with radiopharmaceuticals without resulting in any additional protection of human subjects. It would negatively impact on the progress in the field of radiopharmaceuticals, also required as imaging biomarkers and companion diagnostics. Therefore, radiopharmaceuticals should either be exempted from the scope of the guideline as described above or an additional chapter addressing the specific properties of both diagnostic and therapeutic radiopharmaceuticals and the resulting consequences in a First Iin Human or early phase Clinical Trial should be added.	

2. Specific comments on text

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
68	30	**Comments:** This guidance should also be addressed to investigators and members of ethics committees as well as sponsors.	Accepted. Text amended
68-70	42	**Comments**: The Guideline may not only be helpful for sponsors in the planning and management of early-clinical trials, but also be of assistance to Phase I Units, CROs and clinical investigators. **Proposed change:** Add: <u>The Guideline may also be helpful for Phase I Units, CROs and clinical investigators contracted by sponsors with the conduct of such trials.</u>	Accepted. Text amended
71-74	3	**Comments:** Executive Summary: as summarized (lines 71-74), strategies for mitigating and managing risks **do not** explicitly mention study-design separately from the conduct of the designed CT. See however science-led (line 99). **Proposed change:** Make reference @ lines 71-74 to need to refer also to line 99.	Accepted. Text amended

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
71-74	49	**Comments:** In the draft guidelines' Executive Summary (lines 71-74), strategies for mitigating and managing risks do not explicitly mention study-design separately from the conduct of the clinical trial. We believe the EMA guidelines ought to discuss new (c. past 20 years) designs which maintain the rule that each cohort corresponds to a dose increment but have more flexibility in the number of subjects on placebo, or even on lower doses, within that cohort[1], and should encourage investigation into finding better designs for first-in-human trials. [1]Some of these are described briefly in (a) Senn, S. *et al.* [ibid] (2007) 'Statistical issues in first-in-man studies', available at: http://www.rss.org.uk/Images/PDF/publications/rss-reports-statistical-issues-first-in-man-studies-2007.pdf There are more details in (b) Senn, S. (1997) *Statistical Issues in Drug Development*. Wiley: Chichester; and (c) Bailey, R.A. (2009) Designs for dose-escalation trials with quantitative responses (with discussion). *Statistics in Medicine* 28: 3721–3760.	Not accepted. Too specific detail.
76	30	**Comments:** The introduction should state why FIH/early CTs are done, rather than providing this information mixed into the main text (e.g. line 337). The comment (currently line 432) that MTD trials are not ethical needs to be stated in the introduction since many trials currently have MTD as the primary outcome. It should also include an explanation as to why some studies are performed in patients rather than healthy volunteers. **Proposed change:** The purpose of FIH trials is to take a medicine into humans for the first time, to study the human pharmacology of the IMP, and to compare it's *in vivo* effects in humans (clinical studies) with it's effects in animal and human tissue studies (non-clinical studies). Safe use results from increased understanding of the IMP. Trials should not be designed to identify the maximum tolerated dose; although there may be studies in which identifying the MTD is justified, it must not be the	Partly accepted. Text amended to define the purpose of FIH trials.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		aim of the study in healthy volunteers. In some cases, FIH trials will be conducted in patients as opposed to healthy volunteers. Particular circumstances where that may be appropriate include…… Traditionally, FIH CTs were performed with……	
76 ff	43	**Comments:** There is no differentiation between oncology and other disease areas; the language seems to contrast with common principles of oncology clinical trials (e.g. definition of a maximum dose vs defining a potential dose range).	Accepted.
82	9	**Comments:** Certain patient populations: is this referring to phase 2 studies? Are these trials also in the scope of this guideline?	Accepted. Text amended.
82	47	**Comments:** What is meant by “certain patient populations”? This implies not all patient populations, but some subset that may need defining. Or is this referring to phase-2a studies and are these studies in the scope of this guideline?	
82-83	51	**Comments:** BIO believes it would be helpful for the guideline to further specify high-morbidity and high mortality disease states such as advanced stage cancers.	Not accepted.
82-84	3	**Comments:** Clear statement (lines 82-84) is welcome that: “The aim should always be the safety and well-being of trial subjects, whether patients or healthy individuals”	Accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
82-84	9	**Comments:** Clarify: is this the primary aim for the investigator? Or does this refer to the aim of the guideline or the protocol?	Accepted. Text amended.
83	47	**Comment:** Unclear language. **Proposed change:** Replace by "the aim should always be to evaluate the safety/tolerability **and pk** across a pre-defined **exposure** range whilst ensuring the safety and well-being…"	Partly accepted. Text amended.
83-84	14	**Comments:** "The aim should always be the safety and well-being of the trial subjects, whether patients or healthy individuals." This is reductive, as the aim of the study is typically to collect information on the safety and tolerability of a new therapeutic. **Proposed change:** Suggest adding the text from the current guideline ("..., **and the value of what can be learned from the clinical trial**.").	Partly accepted. Text amended.
83-84	30	**Comments:** Safety is not the aim of these studies. The aim (or objective) is to study the pharmacology, pharmacokinetics, safety and tolerability of the IMP in humans for the first time. Safety is a priority for study design and operation but is not the aim of the study (if that was the case FIH studies would never be done since there is always some element of risk, which must be minimised through good design). Therefore, remove the restricting comment. **Proposed change:** … populations. The safety and well-being of the trial subjects, whether patients or healthy individuals, should always be	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		the priority of the researchers and underpin the trial design.	
83-84	41	**Comments:** The statement here that "The aim should always be the safety and well-being of the trial subjects" is misleading and should be reworded. Although the safety of trial participants should always be of primary importance, this should not be stated as the aim of the study. The main objective of conducting a FIH or early phase trial is to investigate the effects of a drug when given to humans, which includes the safety profile, but importantly also includes the human pharmacology.	Partly accepted. Text amended.
83-84	42	**Comments:** Additional detail underlined **Proposed change:** The aim should always be the safety and well-being of the trial subjects, whether patients or healthy individuals, and the avoidance of unacceptable levels of toxicity.	Partly accepted. Text amended.
83-84	50	**Comments:** The statement should be refined, as the "aim" in first-in-hum (FIH) and early clinical trials is to explore safety, tolerability, and PK. **Proposed change:** "The aim ~~should always be~~ ***is to explore*** safety ~~and well-being of the trial subjects, whether patients or healthy individuals~~**, *tolerability, and pharmacokinetics in way that does not unreasonably jeopardize the well-being of the trial participants.***"	Partly accepted. Text amended.
85-102	26	**Comments:** These lines (and the rest of the draft guideline) focus on risks posed by the investigational medicinal product (IMP), but	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		risks during early studies do not only come from the IMP. Several healthy volunteers have died due to challenge agents/concomitant medication. For these a similar assessment has to be done as for the IMP. Also, invasive study procedures such as CSF sampling, catheterisation, BAL and endoscopy may involve risks. **Proposed change:** Add text to clarify that risks associated with study procedures and other medication/challenge agents used in the study must also be evaluated and appropriate mitigations put in place.	
90-91	18	**Comments:** The reference to predefined maximum dose in Section 1. Introduction is inconsistent with later references which refer to exposure. We suggest the text is amended accordingly. **Proposed change:** From Special attention should be given to the estimation of the initial dose to be used in humans and to the subsequent dose escalations to a predefined maximum dose. To Special attention should be given to the estimation of the initial dose to be used in humans and to the subsequent dose escalations to a predefined maximum exposure.	Partly accepted. Text amended.
90-91	20	**Comments:** “Predefined maximum dose” should really be “maximum *exposure*.” Given the inherent uncertainty in predicting pharmacokinetic properties in humans, the defining limit should be exposure, rather than dose. This principle is already contained in line 409.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Special attention should be given to the estimation of the exposure reached at the initial dose to be used in humans and to the subsequent dose escalations to a predefined maximum dose exposure.	
90-91	21	**Comments:** The term “predefined maximum dose” could be misinterpreted in this paragraph, although the text later clarifies that “exposure should always be taken into consideration”. In a combined FIH trial human pharmacokinetics are predicted, but not yet known. A maximum dose can be anticipated, but not predefined at the stage of trial design. The maximum dose should for most IMPs be defined as the dose leading to a predefined maximum permitted exposure. Maximum dose increments leading from starting dose to maximum exposure should also be defined. For some advanced IMPs, pharmacokinetic exposure may not be relevant, in which case the CT protocol should justify the absence of PK exposure criteria/limits and clarify what criteria will limit the dose selection instead (e.g. pharmacodynamics limits). **Proposed change:** Change text to “Special attention should be given to the estimation of the initial dose to be used in humans, and to the subsequent dose escalations **/ maximum dose increments to a predefined maximum exposure.”**	Partly accepted. Text amended.
90-91	33	**Comments:** The notion of exposure is to be introduced. **Proposed change:** Special attention should be given to the estimation of the initial dose to be used in humans and to the subsequent dose escalations to a predefined maximum dose **/ exposure**.	Partly accepted. Text amended.
90-91	39	**Comments:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Exposure to be introduced right away, as the key driver **Proposed change:** Special attention should be given to the estimation of the initial dose to be used in humans and to the subsequent dose escalations to a predefined maximum dose/exposure.	
90-92	51	**Proposed change:** Special attention should be given to the estimation of the exposure reached at the initial dose to be used in humans and to the subsequent dose escalations to a predefined maximum ~~dose~~ exposure.	Partly accepted. Text amended.
90-93	30	**Comments:** This section could be more explicit in emphasising the critical importance of the starting dose and subsequent dose escalations and its basis in non-clinical PK/PD data and previous experience in humans with drugs of similar mechanism or class. **Proposed change:** Special attention must be given ….	Partly accepted. Text amended.
90-95	23	**Comments:** In order to increase clarity on dose versus exposure and to simplify the text, it is suggested to replace “a predefined maximum dose” by “a predefined maximum exposure” and to delete the remainder of the paragraph as redundant. **Proposed change:** Special attention should be given to the estimation of the initial dose to be used in humans and to the subsequent dose escalations to a predefined maximum **~~dose~~ exposure (Cmax, AUC)**. **~~It should be noted that the expected exposure in humans at a dose to be given, in comparison to the exposure at which certain effects were~~**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		~~**observed in animals or earlier in the study in humans, is considered important. Therefore, whenever dose is mentioned in this guideline, the expected exposure at that dose should always be taken into consideration.**~~	
90-95	26	**Comments:** The words "escalation to a predefined maximum dose" are used and then it is stated that when the guideline says dose it in fact means "expected exposure". This can be simplified. Also, we recommend that the guideline should emphasize that exposure is more relevant than dose. Additionally, evaluation of emerging preclinical data can also lead to the conclusion that the risk of continuation of a FIH study is unacceptable. An example is an IMP with insufficient margin between the highest exposure expected to be needed during the FIH study and exposures at which significant toxicity was observed in animal studies, without sentinel safety biomarkers or without adequate possible measures for risk mitigation. **Proposed change:** Replace “escalation to a predefined maximum dose" with "escalation to a predefined maximum expected exposure". Replace "…..is considered important" by "…. is considered more relevant than the relative dose levels between animals and humans". Add text to clarify that continuous evaluation of emerging preclinical data is necessary and that trial design should be altered or the clinical trial stopped in response to newly identified risks.	Partly accepted. Text amended.
90-95	47	**Comment 1:** Unclear language. Without knowing human PK, the maximum dose cannot be defined. **Comment 2:** Whilst the predicted max dose itself is subject to uncertainty in terms of predicted clearance, volume of distribution, absorption rate and bioavailability, the max dose can be adequately managed proactively in the protocol through defining max exposure (based on NOAEL-associated exposure or MABEL approach). **Comment 3:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Include reference to section 7.2, i.e., to the approaches used for determination of the FIH dose. **Comment 4:** It is unclear whether non-clinical data are intended to be used to predefine the clinical maximum dose (line 91). It is unclear whether this is expected in the pre-clinical toxicity section as line 328 mentions "only serious toxicity should lead to a more cautious approach" whereas in line 684 "a dose stopping criterion addresses the NOAEL in the most sensitive non-clinical species, adjusted by safety factors". At least, the relevance of the most sensitive species for humans should be discussed in the toxicity section and made clear that the severity of the adverse effect and monitorability in humans would allow going beyond the preclinical exposure setting **Proposed change:** "Special attention should be given to ~~the estimation of the initial dose to be used in~~ **establishing or defining** the **exposure at the** first dose to be administered to humans and to the subsequent dose escalations to a predefined maximum **exposure**, using approaches defined in **Section 7.2, 7.3 and 7.4, which includes information from non-clinical (NOAEL, relative seriousness and reversibility of the toxicity and confidence in the PD biomarker) and clinical sources (MABEL prior and emerging clinical data)**."	
91	3	**Comments:** Requirement (line 91) for protocols to nominate and justify a pre-defined maximum dose is welcome.	Partly accepted. Text amended.
93-95	30	**Comments:** It should be emphasised that it is both exposure and effect that should be taken in to consideration **Proposed change:** Therefore, whenever dose is mentioned in this guideline, the expected exposure and effect at that dose must be taken into consideration.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
96-97	36	**Comments:** It should be specified that the programme for an IMP should be developed in accordance with the authorisation of the competent authority(ies) and the opinion of ethics committee(s). **Proposed change:** “In defining an appropriate development programme for an IMP, information on safety needs to be integrated from many sources and reviewed in an iterative process, particularly in accordance with the authorisation of the competent authority (ies) and the opinion of ethics committee(s).”	Not accepted. It was felt there was no need to state this.
96-102	9	**Comments:** Language reads as if this is applicable to “new” studies (FIH) only but this practice should apply to any CT in scope of the guidance, as well as any decision for any cohort or period.	Partly accepted. Text amended.
97-100	36	**Comments:** It should be recalled that strategies for development of a new medicine and experimental approaches should always take into account the safety and well-being of the trial participants. **Proposed change:** “Strategies for development of a new medicine and the experimental approaches used to assemble information relevant to the safety of CTs should always be science-based, and decisions should be made and justified on a case-by-case basis, always taking into account the safety and well-being of the trial participants.”	Partly accepted. Text amended.
98-99	20	**Comments:** It is not clear on what is meant by “should always be science-based, and decisions should be made and justified on a case-by-case basis.”	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Consider revising to, “decisions should be justified based on a rigorous interpretation of the totality of available data.”	
100-102	24	**Comments:** The cases when integrated protocols can be used should be detailed.	Partly accepted. Text amended.
100-102	30	**Comments:** Emerging clinical trial data should inform the steps of all trials (including cohorts with a SAD component) not just those with an integrated protocol **Proposed change:** … basis. It is important to remember that data generated during the trial must be used to inform the decision processes for the continuation of dosing.	Partly accepted. Text amended.
100-102	41	**Comments:** The need to use emerging trial data to inform decisions on continuation of dosing is an important principle, but should be extended to include all FIH and early phase studies, and not just those using an integrated protocol.	Partly accepted. Text amended.
100-102	47	**Comments:** In a stand-alone SAD or MAD study, blinded or unblinded review of aggregate safety data from each completed cohort usually informs escalation of the dose of IMP to the next dose level. The statement referring to “integrated” protocols is meant to suggest that safety data available from one component of the study should also inform initiation of other components (e.g. SAD and MAD portions of the study, especially where SAD and MAD cohorts are conducted with an intercalated approach with dose escalation overlapping). **Proposed change:**	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		"In those cases where an integrated protocol is used in a FIH CT, data generated during the trial should also be used to inform the decision to ***initiate a subsequent component (e.g. MAD or food-effect component), or inform the selection of the dose of IMP to be evaluated for components being conducted sequentially or in overlapping fashion, respectively***".	
101	5	**Comments:** 'the data generated' lacks specificity regarding data from which dose level should be used for decisions about a next dose level, only in the main text this is further explained and specified. **Proposed change:** Describe it clearly in one section of the document, but not in the introduction	Partly accepted. Text amended.
102	40	**Comments:** Would it be useful to clarify that it is continue dosing within that integrated protocol. **Proposed change:** ' ... continuation of dosing within that integrated protocol'	Not accepted. No need to state here.
103	9	**Comments:** Definition of a CT in scope of the guidance would be useful. Also throughout the document at some points the combination "FIH / Early CT" is used and on other occasion "Early CT" or just "CT" – suggest to be consistent within the document.	Partly accepted. Text amended.
103	9	**Comments:** Scope: are PET Studies / Microdosing to be added?	Not accepted. No need to state here.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
103-116	9	**Comments:** Comment 1: Do all these requirements apply to all early phase clinical trials? Comment 2: Please define Early Clinical Trial	Not accepted. No need to state here.
103-116	43	**Comments:** Add a clarifying statement in Section 2. Scope that FIH studies in certain settings (i.e. high-morbidity and high-mortality disease states such as advanced stage cancers) fall into the scope of the guideline, however, flexibility should be applied for those settings. Consideration could be given to include more specific information throughout the guideline text to clearly differentiate the requirements of studies in healthy volunteers vs. patients with advanced cancer or life limiting diseases. Alternatively, either the guideline should formally exclude its applicability to such settings and refer to already existing guidelines (e.g. ICHS9); or the development of an addendum to the guideline, specifically addressing requirements for FIH studies in these settings should be considered.	Not accepted. No need to state here.
104-107	9	**Comments:** Language is somewhat confusing, not consistent use of language?	Partly accepted. Text amended.
106	13	**Comments:** To improve reading we propose to put "*in this guideline*" at that start of the sentence.	Partly accepted. Text amended.
106, 107-109	20	**Comments:** "These trials may also include collection of data on food interaction, in different age groups as well as early proof of concept (PoC) or early proof of principle (PoP) parts and bioequivalence of different formulations." This is not in line with statements in line 104 and 105 which indicate that the guideline focusses on first administrations in humans and first knowledge generated in humans. For instance, food interaction studies do not seem to qualify for this. Thus, the	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		definition of early phase CTs (line 106) seems to be broad and requires a more accurate definition.	
106-109	17	**Comments:** Please clarify the scope. The Guideline suggests that the following studies in healthy volunteers would be within scope: • a single-dose food interaction trial – exposure is predicted not to exceed that in previous clinical trials • a trial to compare single- and repeated-dose PK in young and elderly – exposure in elderly subjects is predicted not to exceed that achieved in young subjects in previous clinical trials • a study to compare PK after single doses of old and new formulations of IMP – exposure is predicted not to exceed that in earlier clinical trials. However, those studies should be outside the scope of the guidance unless exposures are predicted to exceed those previously tested in humans. The scope should exclude first-in-human trials of generic small-molecule IMPs. The scope should specify separate criteria for trials comparing biosimilars with their licensed equivalents. Use of sentinel subjects is usually appropriate in FTIM studies of biosimilars, but other requirements do not apply. For example, requirements for non-clinical studies are different, and calculation of MABEL should not be necessary. Proposed change: Please clarify scope, exclude generics and consider special requirements for biosimilars.	Not accepted. Addressed in scope.
106, 107-109	20	**Comments:** "*These trials may also include collection of data on food interaction, in different age groups as well as early proof of concept (PoC) or early proof of principle (PoP) parts and bioequivalence of different formulations.*" This is not in line with statements in line 104 and 105 which indicate that the guideline focusses on first administrations in humans and first	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		knowledge generated in humans. For instance, food interaction studies do not seem to qualify for this. Thus, the definition of early phase CTs (line 106) seems to be broad and requires a more accurate definition.	
106-109	20	**Comments:** In FIH studies formulation comparisons are typically relative bioavailability assessments, not bioequivalence. Suggest add “for example” at beginning of sentence and replace “bioequivalence” with “relative bioavailability,” and also include DDI assessments as an example.	Partly accepted. Text amended.
106-110	21	**Comments:** We suggest either shortening the list of parts that can be one combined protocol, or if an exhaustive list is intended, adding other examples which are commonly part of integrated protocols. **Proposed change:** To add **drug-drug-interactions and ethnic comparisons**.	Partly accepted. Text amended.
107	20	**Comments:** “after SAD or MAD” is confusing; one could interpret this as meaning the guidance does not apply to SAD or MAD **Proposed change:** Delete “after SAD or MAD”	Accepted. Text amended.
107-108	33	**Comments:** DDI, food effect and gender effect studies should be included in the scope of early CTs.	Accepted. Text amended.
107-108	36	**Comments:** In addition to the collection of data on food interaction, trials may also include collection of data on other treatments	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		interaction where relevant, as long as it may happen in practice (especially when it occurs on a routine practice) that the new medicine will be taken or administered with accompanying treatments. **Proposed change:** "These trials may also include collection of data on food interaction and on other treatments interaction where relevant, in different age groups as well as early proof of concept (…)"	
107-109	14	**Comments:** The list of objectives could be construed as exhaustive, and should be made more general. Proposed change: "**For example**, these trials may also include collection of data on food interaction…"	Partly accepted. Text amended.
107-109	18	**Comments:** Reference to drug- drug interaction is made in Section 8.2.2 Integrated protocols but missing from Section 2 Scope. **Proposed change:** From These trials may also include collection of data on food interaction, in different age groups as well as early proof of concept (PoC) or early proof of principle (PoP) parts and bioequivalence of different formulations. To These trials may also include, for example, collection of data on food interaction, drug-drug interaction, in different age groups as well as early proof of concept (PoC) or early proof of principle (PoP) parts and bioequivalence of different formulations.	Partly accepted. Text amended.
107-	39	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
109		Introduce Drug-Drug Interaction and gender **Proposed change:** These trials may also include collection of data on food interaction, Drug-Drug Interaction, in different age groups or sex as well as early proof of concept (PoC) or early proof of principle (PoP) parts and bioequivalence of different formulations	Text amended.
107-109	47	**Comments:** This guidance should be focused on the first SAD and MAD studies with particular emphasis up to the first agreed dose range for humans or a revised range by a substantial amendment. Single and multi-dose DDI and food intake studies would also be permitted in parallel with SAD and MAD as long as they conform to the set dosing limits and have the proper toleration and exposure coverage from already completed cohorts of SAD and/or MAD studies. Early POC and POP studies would be subsequent to SAD and MAD and should not be in the scope of the guidance, unless the POC or POP endpoints are included in the first SAD or MAD studies – and in this instance they would be secondary measures and not the primary purpose of the studies. **Proposed change:** Remove the sentence "These trials may also include collection of data on food interaction, in different age groups as well as early proof of concept (PoC) or early proof of principle (PoP) parts and bioequivalence of different formulations."	Not accepted. The guideline has been revised to take into account the current practice of trials with integrated protocols including food interaction and PoC parts.
107-109	50	**Comments:** Real bioequivalence trials in the FIH study are rather unlikely. **Proposed change:** "These trials may also include collection of data on food interaction, in different age groups as well as early proof of concept (PoC) or early proof of principle (PoP) parts and ~~bioequivalence~~ ***relative bioavailability*** of different formulations."	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
107-109	51	**Comments:** BIO believes that further clarification is needed if the guideline intends sponsors to study bio-equivalence in a FIH study.	
108	40	**Comments:** Would it be useful to clarify that it is continue dosing within that integrated protocol. **Proposed change:** ' ... continuation of dosing within that integrated protocol'	Not accepted.
108	46	**Comments:** On top of "food interaction", the early investigation of a "Drug x Drug Interaction" should also be considered (with safety risk if a significant increase in exposure is observed with the test drug)	Accepted. Text amended.
108-109	32	**Comments:** PoC / PoP seems to be the same, one term can be deleted. If indeed different things are meant, this should be explained in more detail. **Proposed change:** (...) in different age groups as well as early proof of concept (PoC) ~~or early proof of principle (PoP)~~ parts and (...)	Accepted. Text amended.
109	9	**Comments:** Is Bioequivalence part of early clinical trials? Usually only performed in later development	Accepted. Text amended.
109-110	30	**Comments:** It would be useful to expand when and why patients are included into FIH studies with examples instead of stating 'in	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		certain situations' **Proposed change:** These trials are often undertaken in healthy volunteers but can, in certain situations, also include patients. This may include inclusion of a cohort of patients as part of an integrated protocol with healthy volunteers or a FIH study in patients exclusively (for example in oncology, where the drug target is expressed only in patients, or where the principle of minimal risk is not applicable and FIH trials in healthy subjects not ethically justified')	
109-110	51	**Comments:** BIO believes that further specification regarding how this guideline applies to high-morbidity and high mortality disease states such as advanced stage cancers will be useful.	Not accepted. Too specific detail.
110	13	**Comments:** Add "*(e.g. in oncology)"* to the end of the sentence, as this clarifies the "certain situations".	Partly accepted. Text amended.
110	47	**Comments:** Please further Specify how this guideline applies to high-morbidity and high mortality disease states such as advanced stage cancers. As proposed change a clarifying statement in Section 2. Scope could be added that FIH studies in certain settings (i.e. high-morbidity and high-mortality disease states such as advanced stage cancers) fall into the scope of the guideline, however, more flexibility may apply for those settings. Consideration could be given to include more specific information throughout the guideline text to clearly differentiate the requirements of studies in healthy volunteers vs. patients with advanced cancer or life limiting diseases. Alternatively, it could be envisaged to develop an addendum to the guideline, specifically addressing requirements for FIH studies in these settings.	Not accepted. Too specific detail.
114	9	**Comments:** Why are ATMP out of scope? Does it need to be specified this is applicable to biological vs chemical?	Not accepted. ATMPs out of scope because

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			considered too different.
114	20	**Comments:** The agency should clarify in the text that the intent is to apply to novel products and that biosimilars are out of scope as this could potentially be misinterpreted otherwise. **Proposed change:** The guideline applies to all new novel chemical and novel biological IMPs, (excluding biosimilars).	Not accepted. The guideline applies to all new chemical and biological IMPs.
114	47	**Comments:** The agency should clarify in the text that the intent is to apply to novel products and that biosimilars are out of scope as this could potentially be misinterpreted otherwise. Also, please state directly if this guidance applies to Oncology compounds – as written it does not appear to apply to Oncology compounds – an example is the conservative approach to clinical exposure caps vs severe toxicity exposures in animals when Phase 1 for Oncology may be conducted in patients. Furthermore, this guideline currently considers primarily human cellular molecules as pharmacological target, but not pathogen specific molecules (i.e. antibiotics, antivirals, antifungals), for which some aspects and consequences in this guideline do not apply. Similarly, vaccines also do not fit most of the specific elements in this proposes guideline because of their different mechanism of action from small molecule compounds. Therefore, we would propose to add information on this in section 2 “scope” and other relevant sections. **Proposed change:** The guideline applies to all ~~new~~ **novel** chemical and **novel** biological IMPs, **(excluding biosimilars, vaccines, and oncology).** It is of note that this guideline primarily considers (host-) cellular molecules as the pharmacological target of the drug to be investigated and that some aspects and consequences (e.g. MABEL calculation not applicable in healthy volunteers or due to variable susceptibility of pathogens) do not apply for drugs specifically targeting pathogen-specific	Not accepted. The guideline applies to all new chemical and biological IMPs.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		molecules (i.e. antibiotics, antivirals, antifungals).	
114	48	**Comments:** We acknowledge the intent of the guideline to apply equally to all new chemical and biologic IMPs. However with respect to biological IMPs a number of items were noted which warrant greater flexibility or additional clarity. These are noted in the specific comments which follow.	Not accepted. The guideline applies to all new chemical and biological IMPs.
114	51	**Comments:** The draft guideline states, “The guideline applies to all new chemical and biological IMPs.” BIO requests further clarification regarding whether ‘biological IMPs’ include biosimilars.	Not accepted. The guideline applies to all new chemical and biological IMPs.
114-116	10	**Comments:** This guideline currently considers primarily human cellular molecules as pharmacological target, but not pathogen-specific molecules, for which some aspects and consequences in this guideline do not apply. **Proposed change:** Please adjust the guideline accordingly.	Not accepted. The guideline applies to all new chemical and biological IMPs.
114-116	36	**Comments:** The clarification on the link between this guideline and those specifically relating to advanced therapy investigational medicinal products is very welcomed. Support for stakeholders’ guidelines navigation would be increased if clear reference to the concerned guideline is included.	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "While many of the scientific principles included in this guideline apply to advanced therapy investigational medicinal products as well, these products are not included in the scope of this guideline. (For advanced therapy investigational medicinal products, see the European Commission "Detailed guidelines on good clinical practice specific to advanced therapy medicinal products" (ENTR/F/2/SF/dn D(2009) 35810) "	
114-116	47	**Comments:** Please provide reference to the definition for advanced therapy investigational medicinal products and the rationale for exclusion of this category of products is not obvious. **Proposed change:** While many of the scientific principles included in this guideline apply to advanced therapy investigational medicinal products as well, these products are not included in the scope of this guideline **because….please include a rationale here along with examples of Therapeutic area/class. For detailed definitions of advanced therapy medicinal products, refer to Regulation (EC) No 1394/2007 and Directive 2001/83/EC.**	Accepted. Text amended.
114-116	54	**Comments:** See general comment. **Proposed change:** While many of the scientific principles included in this guideline apply to advanced therapy investigational medicinal products **and radiopharmaceutical IMPs** as well, these products are not included in the scope of this guideline	Not accepted. The guideline applies to all new chemical and biological IMPs.
115	20	**Comments:** Reference to "advanced therapy investigational medicinal products" is ambiguous. We recommend using more specific	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		language, such as defining as “cellular therapies, gene therapies and tissue-engineered products.”	
115	45	**Comments:** ATIMPs are noted to be outside the scope of this guideline. Guidance in the area FIH ATIMPs is also needed and we suggest its inclusion in the current guideline, unless separate guidelines are envisaged?	Not accepted. ATMPs are not within scope.
117	47	**Comments:** The EMA Guideline on the investigation of drug interactions (CPMP/EWP/560/95) should be mentioned, as the guidance indicated that high exposures should be studied if possible. Furthermore, this guidance specifies that healthy volunteers should be the typical population under study for such studies.	Not accepted. Too specific detail.
118	53	**Comments:** please consider EU regulation n°536/2014 to be applicable **Proposed change:** ~~which will be~~ repealed by Regulation	Accepted. Text amended.
118-119	26	**Comments:** For clarity, ACRO recommends that the text should state that, when Directive 2001/20/EC is repealed by Regulation (EC) 536/2014, this guideline will continue to apply. **Proposed change:** Make clear that, when Directive 2001/20/EC is repealed by Regulation (EC) 536/2014, this guideline will continue to apply.	Not accepted. No need to state here.
118-	6	**Comments:**	Accepted. Text

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
147		The ICH M7 guideline should be added to paragraph 3, as it is also valid for products under development. **Proposed change:** After line 147, add: "Assessment and Control of DNA reactive (mutagenic) Impurities in Pharmaceuticals to limit potential carcinogenic risk (ICH M7)"	amended.
121	23	**Comments:** Proposal to add ICH M7 as relevant reference in section 3 as this provides the legal basis to support section 5.2 Qualification of the material used. **Proposed change:** **Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (ICH M7).**	Accepted. Text amended.
125-147	13	**Comments:** It is proposed to order these guidelines per topic (for example, anticancer guidelines grouped together).	Accepted. Text amended.
127-130	46	**Comments:** These guidelines are already embedded in Eudralex Vol 10 above, so consider deleting.	Accepted. Text amended.
140	46	**Comments:** These guidelines are already embedded in Eudralex Vol 10 above, so consider deleting.	Accepted. Text amended.
144-145	47	**Comments:** Considering that ICH-S7B (non-clinical) is included, it would be appropriate to also add reference to ICH-E-14 including the 2015 Q&A document, which is quite relevant here because it includes recommendations for ECG monitoring in early	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		clinical development (e.g. PK/QT modelling from SAD and MAD studies. **Proposed change:** Add reference to ICH E14 including the Q&A document	
148	53	**Comments:** Not only Factors of risk but also Patient Selection Strategy can make a consideration to design First-in-human CT. Is it an issue the Guideline may address?	Accepted. Text amended.
149-151	25	**Comments:** The guidance should indicate more clearly where this information should be presented. The guideline mentions *These factors should be addressed appropriately for all FIH/early CTs in the sponsor's CTA.* We believe that potential risks factors and risk mitigation strategies must be clearly discussed in the Investigator Brochure and Protocol, as these are the official documents used by the ethics committee, investigators and clinical staff. **Proposed change:** Line 150-151: These factors should be addressed appropriately for all FIH/early CTs in the Investigator Brochure and the Protocol.	Not accepted. The term CTA refers to the total package submitted to Compaetent Authorities to approve a trial.
149-151	42	**Comments:** While the guideline requests that potential risk factors should be addressed in the sponsor's CTA, no information is provided in which document exactly the information should be included. This also applies to the subsections 4.1 – 4.4. **Proposed change:** Specify the document(s) where the potential risk factors should be addressed. With recent issuance of ICH E6 R2 and the addenda (section 5) in which QRM is being applied to GCP, simply stating	Not accepted. The term CTA refers to the total package submitted to Compaetent Authorities to

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		"appropriate risk mitigation strategies" does not impart guidance to the Industry. It is recommended that EMA include at least some examples of "appropriate risk mitigation strategies" and ideally connect with principles of QRM noted in ICH E6 R2. It is recommended that EMA expand the narrative here on risk mitigation strategies.	approve a trial.
149-154	47	**Comment 1:** If a study with integrated design is meant to enrol patient volunteers in one or more additional cohorts after initial exploration of safety, PK, and PD of the IMP in healthy subjects, then the nature of the underlying disease and other subject characteristics may be relevant in those instances where this may impact the exposure after administration of a single or multiple doses or interpretation of safety, PK, and PD data. **Comment 2:** The risks described in §4.1 MOA and §4.2 Nature of Target also apply to major metabolites of small molecules. **Proposed change:** "When planning FIH/early CTs, sponsors and investigators should identify the potential factors of risk and apply appropriate risk mitigation strategies **keeping in mind characteristics of patient volunteers to be enrolled relative to healthy subjects, if applicable".** These factors should be addressed appropriately for all FIH/early CTs in the sponsor's CTA. ***For small molecules, the risk factors described below should also be considered for major metabolites.*** Factors of risk …. '"	Partly accepted. Text amended.
150-151	32	**Comments:** The information on risk factors should also be available for investigators and should therefore be provided in the relevant study documentation i.e. protocol and IB. **Proposed change:**	Not accepted. The term CTA refers to the total package submitted to

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		These factors should be addressed appropriately in the sponsor's CTA as well as in the relevant study documentation i. e. protocol and investigator's brochure for all FIH/early CTs. ~~in the sponsor's CTA.~~	Compaetent Authorities to approve a trial.
151	9	**Comments:** What is exactly meant by CTA? Are these factors part of CTA? Or does this refer to the protocol?	Not accepted. The term CTA refers to the total package submitted to Compaetent Authorities to approve a trial.
151	9	**Comments:** Risk assessment/mitigation to be included in CTA?	Not accepted. The term CTA refers to the total package submitted to Compaetent Authorities to approve a trial.
152-154	30	**Comments:** Factors of risk should also include the population being studied – for example in patient groups one might consider the risk posed by even well controlled comorbidities. **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Factors of risk may be derived from … and the population in which the study will be conducted.	
152-154	42	**Comments:** Additional detail **Proposed change:** Factors of risk may be derived from particular knowledge or lack thereof regarding the mode of action, the nature of the target, the relevance of animal models and/or findings in non-clinical safety studies. A risk assessment should be performed to optimize the balance of safety, ethics, and trial objectives prior to the initiation of study start.	Partly accepted. Text amended.
154	9	**Comments:** Factors should also include clinical information once available.	Partly accepted. Text amended.
155	46	**Comments:** Note that for small molecule, this section implicitely refers to the NCE itself but not to possible metabolite. It might be interesting to consider possible metabolite(s) more explicitely.	Not accepted. Too specific details.
155-186	12	**Comments:** The first paragraph of the section gives appropriate general guidance to Sponsor on how to address potential factors of risk associated with the mode of action (lines 156-163). The examples cited in this section (lines 164-186), however, are unnecessary, because they are too specific for a certain type of IMP and do not apply to every single compound. **Proposed change:** Remove examples (lines 164-186). ~~"For example, the following aspects might require special attention:~~	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		~~• A mode of action that involves a target that is associated to multiple signalling pathways (target with pleiotropic effects), e.g. leading to various physiological effects, or targets that are ubiquitously expressed, as often seen in the immune or nervous system.~~ ~~• A biological cascade or cytokine release including those leading to an amplification of an effect that might not be sufficiently controlled by a physiologic feedback mechanism (e.g. in the immune system or blood coagulation system).~~ ~~• A mode of action that involves irreversible or long lasting binding to the primary target, either due to pharmacological action or the PK profile of the compound. For instance, if the duration of the pharmacological activity is linked to regeneration of the receptor, rather than being related to the PK profile of the molecule.~~ ~~When analysing risk factors associated with the mode of action, aspects to be considered may include:~~ ~~• Previous exposure of humans to compounds that have similar or related modes of action.~~ ~~• The usefulness of PD data following repeated dosing testing. While single dose PD data can be used for an initial interpretation of the potential outcome of multiple dosing, consideration should be given to conducting repeated dose pharmacology studies or to include PD endpoints in repeated dose toxicity studies.~~ ~~• Evidence from animal models (e.g. knock-out, transgenic or humanised animals) for the potential risk of serious pharmacologically mediated toxicity.~~ ~~• Novelty of the molecular structure of the active substance(s), for example a new type of engineered structural format, such as those with enhanced receptor interaction as compared to previously characterised compound(s). "~~	
156-163	20	**Comments:** While consideration of MOA is valuable for assessing risk and the effects and mechanisms mentioned in this paragraph seem reasonable, this discussion omits consideration of inter-species translations of mechanism and effects. In many cases this translation is unknown or not well understood. In particular, knowledge of the translatability of the cascade of cytokines and immune endpoints can be limited. Additional comments or context should be added regarding how impact	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		of translatability, or lack of, should be considered in the decision to initiate a FIH CT.	
157-158	32	**Comments:** Last part of the sentence can be deleted, since the "target" is discussed in section 4.2. **Proposed change:** (…) mode of action~~, as well as the characteristics of the target.~~ (…)	Partly accepted. Text amended.
158	20	**Comments:** In terms of mode action it is also important to understand the homology and conservation of the target expression and physiology amongst mammals and human to translate safety findings. **Proposed change:** "This includes the nature and intensity of the effect (e.g. extent, amplification, duration, (ir)reversibility) and other mechanistic effects of the IMP on the intended target(s) and potential off-targets. Understanding the homology and conservation of the target expression and physiology amongst mammals and human is also an important for safety translatability. The type of …."	Partly accepted. Text amended.
158	51	**Comments:** In terms of mode action it is also important to understand the homology and conservation of the target expression and physiology amongst mammals and human to translate safety findings. **Proposed change:** This includes the nature and intensity of the effect (e.g. extent, amplification, duration, (ir)reversibility) and other mechanistic effects of the IMP on the intended target(s) and potential off-targets. Understanding the homology and conservation of the target expression and physiology amongst mammals and human is also an important factor for safety	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		translatability.	
158	53	**Comments:** Is the Guideline expecting to address additional cohorts after the MTD is reached? This may be considered for oncology drugs. Therefore the sentence may add : "… and the right population to the right indication"	Not accepted.
159	47	**Proposed change:** Add to duration also: onset of effect (might be delayed, e.g., hysteresis)	Partly accepted. Text amended.
160	33	**Comments:** Dose exposure relationship is not considered. **Proposed change:** The type and steepness of the dose response and of the dose exposure relationship…	Partly accepted. Text amended.
160-163	47	**Comments:** The relevance of the "experimental systems" for the human situation should also be considered when investigating the dose response relationship. **Proposed change:** The type and steepness of the dose response relationship **is of particular importance and needs to be understood in human relevant experimental systems and at exposures relevant for clinical studies. Dose response curves can be linear or non-linear (plateau with a maximum effect, over-proportional increase, U-shaped, bell-shaped, time dependent, or pulsatile).**	Partly accepted. Text amended.
164	51	**Comments:**	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		BIO believes it is currently unclear if a compound acts as an agonist whether it would require special attention similar to the examples listed. Additional clarification regarding this case would be helpful.	detail.
165	47	**Proposed change:** Type-o: target that is associated ~~to~~ with multiple signalling pathways	Accepted. Text amended.
165-174	13	**Comments:** The use of examples to illustrate how mode of action can contribute to risk could aid to further clarify this section.	Not accepted. Too specific detail.
167-170	23	**Comments:** It seems more appropriate to distinguish innate and acquired immunity. In these cases, it is more accurate to refer to the innate immune system. **Proposed change:** "…or targets that are ubiquitously expressed, as often seen in the **innate** immune or nervous system." And "…(e.g. in the **innate** immune system or blood coagulation system)."	Not accepted. Too specific detail.
171	47	**Comments:** Antibodies by their nature will have long-lasting effects because of their binding properties and PK. Please clarify what kind of "special attention" would be required here. Also, note that many animal models do not routinely characterize the duration of effect or the time to return to baseline after exposure; that would create a significant burden.	Partly accepted. Text amended.
175	5	**Comments:**	Not accepted. Requirement is

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		"may include" is non-restrictive language **Proposed change:** To be replaced by “if applicable, must include xxxx”. And in the case of not applicable it should be explained in the protocol.	not restrictive.
175-185	47	**Comment 1:** Consider adding as an additional risk factor, evidence from human genetic data if mutations have been described in the gene in humans. **Comment 2:** The value of repeated dose pharmacology studies to assess and PD endpoints is not always value added. It is also not clear of the value for adding PD endpoints to toxicity studies where doses achieve high therapeutic margins. This could lead to difficulty in interpreting PD from toxicity and potentially complicate the main purpose of the toxicity study. If the point of repeat dose pharmacology studies is to evaluate the sustainability of a PD response, the pharmacologic models may be insufficiently similar to humans to achieve the desired assessment. For a FIH CT, information of this sort may not be of value to collect and the expectation to do so could add time and cost for minimum return value. The inclusion of these studies should only be recommended in situations where the results would impact safety considerations. **Proposed change:** “When analysing risk factors associated with the mode of action, aspects to be considered may include: • Previous exposure of humans to compounds that have **same,** similar or related modes of action. • The usefulness of PD data following repeated dosing testing. While single dose PD data can be used for an initial interpretation of the potential outcome of multiple dosing, consideration should be given to repeated dose pharmacology studies or to include PD endpoints in repeat dose toxicity studies **where the results would**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		impact safety considerations. • **Evidence from human genetic mutations in relevant targets.**	
177	20	**Comments:** "Should include compounds with the same MoA as well." **Proposed change:** Previous exposure of humans to compounds that have the same, similar, or related modes of action	Accepted. Text amended.
177	51	**Comments:** BIO believes this section should include compounds with the same MoA as well. **Proposed change:** Previous exposure of humans to compounds that have the same, similar, or related modes of action. Additionally, please see our related comment at lines 343-344.	Accepted. Text amended.
178	30	**Comments:** 'The usefulness of PD data following repeated dosing testing' – correct grammar **Proposed change:** 'The usefulness of PD data following repeated dosing'.	Accepted. Text amended.
178-181	17	**Comments:** Section 4.1 Mode of action. It's not clear whether this refers to non-clinical PD data, clinical PD data or both. If clinical data are included in 'single dose PD data', the reference to repeated dose pharmacology studies doesn't make sense.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Clarify which data are nonclinical and which are clinical.	
178-181	20	**Comments:** The value of repeated dose pharmacology studies to assess and PD endpoints is not always value added. The addition of PD endpoints to toxicity studies may also have limited value where doses achieve high therapeutic margins. This could lead to difficulty in interpreting PD from toxicity and potentially complicate the main purpose of the toxicity study. If the point of repeat dose pharmacology studies is to evaluate the sustainability of a PD response the pharmacologic models may be insufficiently similar to humans to achieve the desired assessment. For a FIH CT, information of this sort may not be of value to collect and the expectation to do so could add time and cost for minimum return value. The inclusion of these studies should only be recommended in situations where the results would impact safety considerations.	Partly accepted. Text amended.
178-181	34	**Comments:** While PD markers can be followed in toxicology species for target knock-down or inhibition mode of action, the ability to determine PD effects for molecules with agonist or upregulation is limited or not feasible in a wild type background and should be considered as part of this guidance.	Partly accepted. Text amended.
178-181	39	**Comments:** In some case, MAD not necessary when PD effect is prolonged (e.g. Monoclonal antibodies) **Proposed change:** Add "<u>For compounds with a prolonged PD effect in the efficacious dose range at single doses (e.g. monoclonal antibodies), a specific dedicated multiple ascending dose study may not be necessary</u>"	Partly accepted. Text amended.
178-181,	47	**Comments:** Please clarify if "PD" includes ligand displacement PET or other imaging. We consider ligand displacement PET imaging as	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
285		a special case of PK, rather than PD. **Proposed change:** Please clarify what is meant by PD relative to PET vs target engagement	detail.
178-181, 285	50	**Comments:** While the value of repeat dose studies is clearly appreciated there should also be recognition that the translation of the development of tolerance in non-clinical species many not be quantitatively translatable to humans particularly in therapeutic areas where there is a subjective component to response (e.g. pain, depression).	Not accepted. Too specific detail.
178-181	51	**Proposed change:** BIO suggests the following sentence at the end of this bullet For compounds with a prolonged PD effect in the efficacious dose range at single doses (often for monoclonal antibodies), a specific dedicated multiple ascending dose study may not be necessary.	Partly accepted. Text amended.
180-181	31	**Comments:** The repeated dose studies are in general conducted in line with M3 which does not mention this concept. PD studies are also usually conducted in disease models etc. and not in healthy animals, relevance of PD investigations in healthy animals seem questionable. Please clarify expectations.	Partly accepted. Text amended.
182, 187	20	**Comments:** It is unclear if Sponsors are being asked to generate data or if literature-based data is okay. Context should be added regarding expectation whether the desired information is to be generated in animal models or if literature-based support is sufficient.	Accepted. Text amended.
182-	34	**Comments:**	Not accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
183		While we always utilize animal models in development and understanding of pharmacology and toxicology, it is important to remember that additional adaptive changes may occur and later generations of transgenic animals may not be translatable to human effects. **Proposed change:** Please add language to ensure risks are considered.	Too specific detail.
182-183	47	**Comments:** Please clarify that the animal models being described here are only animal models that have been genetically modified. We recognize that there are animal models that do not use genetic modification. If both genetically modified and non-genetically modified animal models are being described, please clarify. **Proposed change:** "Evidence from **genetically-modified** animal models (eg, knock-out, transgenic or humanised animals) for the potential risk of serious pharmacologically-mediated toxicity	Not accepted. Too specific detail.
182-183	51	**Comments:** BIO notes that if the molecule targets a single specific kinase with low specificity, it is important to take into account the potential side effects at supra-pharmacology exposure activating or inhibiting other kinases. **Proposed change:** Evidence from animal models (e.g., knock-out, transgenic or humanised animals) for the potential risk of serious pharmacologically-mediated toxicity or supra-pharmacology responses <u>including off-target activities.</u>	Not accepted. Too specific detail.
183	20	**Comments:** To take into account effects related to close targets example if the molecule targets a single specific kinase with low	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		specificity, it is important to take into account the potential side effects at supra-pharmacology exposure activating or inhibiting other kinases. **Proposed change:** "Evidence from animal models (e.g. knock-out, transgenic or humanized animals) for the potential risk of serious pharmacologically-mediated toxicity or supra-pharmacology responses".	detail.
184-185	20	**Comments:** Unclear what constitutes "novelty of the molecular structure of the active substance(s)." Novelty is considered requisite for intellectual property, thus could be applicable for all IMPs. **Proposed change:** "Novelty of the molecular ~~structure of the active substance(s), for example a new type of engineered structural format~~ mode of interaction of the compound and receptor, such as those with ~~enhanced receptor interaction~~ covalent modification of the receptor, as compared to previously characterized ~~compound(s)~~ molecular modes for this target"	Partly accepted. Text amended.
184-186	22	**Comments:** "Novelty of the molecular structure of the active substance(s), for example a **new type of engineered structural format**, such as those with enhanced receptor interaction as compared to previously characterised compound(s). **Proposed change:** Please reword example – bold underlined part is not clearly stated in pharmacology terms.	Partly accepted. Text amended.
184-186	47	**Comment 1:** While such comparison to well-characterized compounds in the public domain is possible the potential to compare to	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		proprietary compounds is unavailable, for compounds not owned by the sponsor, and potentially cumbersome for those analogous to the compound of interest. In the aspects to be considered and that might require special attention please consider adding a bullet to assess if the potential risks can be monitored, are expected to be reversible, and if those are considered to be treatable without significant sequelae **Comment 2:** Novelty is considered requisite for intellectual property, thus could be applicable for all IMPs. Therefore, it is the novelty of the mode of action that is important. **Proposed change:** "Novelty of the **mode of interaction** ~~molecular structure~~ of the active substance(s), for example …….	
187	46	**Comments:** Same comment regarding parent drug and metabolite(s) **[**note that for small molecule, this section implicitely refers to the NCE itself but not to possible metabolite. It might be interesting to consider possible metabolite(s) more explicitely.]	Not accepted. Too specific detail.
187	47	**Proposed change:** 4.2. Nature of the target Beyond the mode of action, the nature of the target itself might impact on the potential risk inherent to the initial administrations to humans. Sponsors should carefully review and discuss significant or likely target-related risks associated with the intended target in humans, which should include the following aspects, based on the available data, and **where appropriate, this evidence can be literature based**:	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
187-201	12	**Comments:** The suggested aspects to be discussed, regarding the target's nature related risks, are too specific and do not apply to all IMPs. In addition: • the polymorphisms of a target within animal species and specifically in the strains used in the nonclinical studies are generally not known. • the statement "Sponsors should carefully review and discuss…**the extent of available knowledge** on the structure, tissue distribution… **If such data are limited, this should be highlighted**" is ambiguous. It is not clear to which extent the data are considered limited and may lead to unnecessary use of animals (inconsistent with 3Rs). **Proposed change:** Beyond the mode of action, the nature of the target itself might impact ~~on~~ the potential risk inherent to the initial administrations to humans. Sponsors should carefully review and discuss any potential risks associated with the intended target in humans, which should include the following aspects, based on the available data: • ~~The extent of the available knowledge on~~ the structure, tissue distribution ~~(including expression in/on cells of the human immune system)~~, cell specificity, disease specificity, regulation~~, level of expression~~, and biological function of the human target~~ including "down- stream" effects~~, and how it might vary between individuals in different populations of healthy subjects and patients. ~~If such data are limited, this should be highlighted.~~ • If possible, a description of polymorphisms of the target in ~~relevant animal species and~~ humans, and the impact of any such polymorphisms on the pharmacological effects of the medicinal product. • Potential off-target effects, with particular focus on, but not limited to, targets closely related/similar to the intended one.	Partly accepted. Text amended.
189-190,	47	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
203-205		"Sponsors should carefully review and discuss any potential risks associated with the intended target in humans, which should include the following aspects…" And "The sponsor should discuss the relevance of the non-clinical models to humans taking into account the target, its structural homology, distribution, signal transduction…." Is the expectation that the sponsor specifically address all these issues in the background of the protocol/IB/CTA?	Text amended.
189-191	20	**Comments:** This section seems too broad. "Any potential risks" does not provide enough clarity around significance or probability of an undesired event. **Proposed change:** Change "any potential" to "likely and important potential risks."	Partly accepted. Text amended.
192-196	22	**Comments:** Bullet point contains potential requirements that are difficult to obtain from the non-clinical documentation. This request is more relevant as a topic of RMP after approval rather than during pre-clinical development: "…. and biological function of the human target including "down- stream" effects, **and how it might vary between individuals in different populations of healthy subjects and patients."** **Proposed change:** Please reconsider/delete bold underlined section.	Partly accepted. Text amended.
193	47	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		For targets which are located behind the BBB, factors related to brain penetration will need to be considered, (e.g. interaction with PgP).	Text amended.
198-199	47	**Comments:** With regard to "…the impact of such polymorphisms on the pharmacological effects of the medicinal product." – in many cases, this information will not be available and the text should be modified to acknowledge this. **Proposed change:** Modify the final sentence to read: "……of the medicinal product**, where such information is available.**"	Not accepted. No need to state.
200-201	20	**Comments:** *"Potential off-target effects, with particular focus on, but not limited to, targets closely related/similar to the intended one."* Lines 286-287: "*Primary PD studies should address the mode of action related to therapeutic use and provide knowledge on the interaction of the IMP with the intended target as well as with related targets*." What are (closely) related targets: same mode of action? Binding of similar molecular entities?	Partly accepted. Text amended.
200-201	26	**Comments:** Section 4.2 concerns the nature of the target, whereas this bullet point concerns off-target effects. ACRO therefore recommends moving this bullet point to the previous section (4.1) on mode of action. **Proposed change:** Move this bullet point to section 4.1.	Partly accepted. Text amended.
200-	47	**Comments:**	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
201		This is of particular relevance for small molecules as opposed to biologics, which are nearly always very target-specific. Also, clarify what are closely related targets **Proposed change (if any) 1:** **In case of small molecules,** potential off-target effects, with particular focus on, but not limited to, targets closely related/similar to the intended one – **e.g. receptor or enzyme subtypes – PDE3 vs PDE4 when PDE4 is the primary target.**	detail.
202	46	**Comments:** Not clear for the reader if this small section refers to "efficacy" and/or "safety" animal models. Would be good to clarify.	Partly accepted. Text amended.
202-205	12	**Comments:** It is not clear whether this paragraph is relative to the relevance of the animal species for the pharmacodynamic or toxicologic evaluation. The aspects to be discussed are based on “on-target” effect consideration only; although the aim of nonclinical safety evaluation is to address on-target and off-target safety issues, consistent with ICH guidelines. • This is particularly important since off-target toxicities represent a large part of the toxicities identified in nonclinical studies and they are very informative for the risk assessment in early clinical development. Also, the recommendations regarding the aspects to be discussed relative to the relevance of the animal model are too prescriptive and do not apply to all IMPs. For example, in most cases, the data on signal transduction pathway and distribution are not available in both animal species, especially for toxicology studies. The overly prescriptive guidance may lead to default selection and unnecessary use of the non-human primate as the non-rodent toxicology species only because more data are available in this species. **Proposed change:** The sponsor should discuss the relevance of the non-clinical pharmacological and toxicological models to humans taking	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		into account the nature and the pharmacology of the target, the metabolism and other PK aspects.~~its structural homology, distribution, signal transduction pathways and the nature of pharmacological effects~~	
202-205	47	**Comments:** Paragraph 4.3 and 4.4: relevance of animal species and models is discussed in a lot more detail in 6.1, and 6.5 respectively; suggest to delete this paragraph; avoids duplication and confusion.	Accepted. Text deleted.
203	5	**Comments:** This paragraph states that 'the sponsor should discuss', but this is not specific enough. **Proposed change:** "The sponsor should discuss with the investigator and should document" needs to be added here.	Partly accepted. Text amended.
203-205	26	**Comments:** It is unclear whether the discussion of the relevance of the non-clinical models is applicable to the pharmacodynamic studies and safety studies or to the pharmacodynamic studies alone. ACRO recommends that this is clarified. **Proposed change:** Add a statement to clarify the scope of the discussion of the relevance of the non-clinical models.	Partly accepted. Text amended.
204	30	**Comments:** Researchers must also take into account the temporal expression of the target, not just the location. For the Tegenero compound, subsequent research showed that the target was downregulated in some T cell subsets in adults of the monkey species used for non-clinical studies, unlike in humans. Its presence on T cells of the adult volunteers studied in the FIH was one reason for the severe activation of the immune system seen in these volunteers	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: … target, its structural homology, its temporal expression and distribution, age of animals, signal transduction pathways and the nature of …	
205	20	**Comments:** The relative potency of the molecule cross-species against the target is not really covered anywhere but a lower potency against the tox species than against the human target could be significant for risk assessment. **Proposed change:** "…the nature of the pharmacological effects (see Section 6.1). Differences in the relative potency of the molecule against the target in the species used for pharmacology/toxicity studies and the intended patient population should also be considered."	Partly accepted. Text amended.
207	30	**Comments:** The findings should come from both toxicology studies and safety pharmacology. **Proposed change:** The findings in non-clinical safety studies, including both toxicology and safety pharmacology, that are considered to be relevant ….	Partly accepted. Text amended.
207-208	10	**Comments:** The need for an integrative assessment of all non-clinical data should be described more specifically. Section 4.4 should start with the following sentence: **Proposed change:** "A weight-of-evidence approach based on the non-clinical and emerging clinical results as well as on available information	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		from other sources, as applicable, e.g. information on effects observed for the class of substance to be studied, should be pursued to support an integrated risk assessment. This should be continuously reviewed in an iterative process during further development."	
207-208	20	**Comments:** There are cases where findings are deemed of little or no relevance to humans. For example, ADA mediated hypersensitivity reactions to a human protein IMP in a rodent species. At least a mention of providing justification for non-relevance should be added, and if possible a discussion of common situations/reasons a finding may be considered non-relevant to humans.	Partly accepted. Text amended.
207-208	33	**Comments:** An integrative, iterative and continuous assessment of all non-clinical data should be described more specifically.	Partly accepted. Text amended.
207-208	47	**Comments:** There are cases where findings are deemed of little or no relevance to humans. For example, ADA mediated hypersensitivity reactions to a human protein IMP in a rodent species. At least a mention of providing justification for non-relevance should be added, and if possible a discussion of common situations/reasons a finding may be considered non-relevant to humans. **Proposed change:** (add after line 208) **Cases where safety findings are of little or no relevance to humans (e.g. ADA mediated hypersensitivity reactions to a human protein IMP in a rodent species) should also be discussed.**	Partly accepted. Text amended.
207-208	51	**Comments:** There are cases where findings are deemed of little or no relevance to humans. For example, antidrug antibody (ADA) mediated hypersensitivity reactions to a human protein IMP in a species. BIO believes that a mention of providing	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		justification for non-relevance should be added, and if possible a discussion of common situations/reasons a finding may be considered non-relevant to humans.	
208	9	**Comments:** 4.5 or 5.2: additional interventions Interventions may also cause risks. you may want to cover this as well	Partly accepted. Text amended.
208-209	9	**Comments:** Suggest to add a section 4.5 on clinical data (see comment associated with line 154)	Partly accepted. Text amended.
209-231	30	**Comments:** The formulations used in non-clinical studies frequently differ from those planned in man (rodents can't take capsules/tablets; exposure to some excipients used in toxicology studies is restricted in man, etc.). The potential impact on exposure and, therefore, effect, at the starting dose should be considered. **Proposed change:** ***5.4 Formulations used in non-clinical studies*** The formulations used in non-clinical studies frequently differ from those planned in humans (for example, rodents can't take capsules/tablets and exposure to some excipients used in toxicology studies is restricted in humans). The potential impact on exposure and, therefore, effect, at the starting dose should be considered.	Partly accepted. Text amended.
210-211	32	**Comments:** Physico-chemical characterisation may be limited for biologicals compared to chemicals. Biological characterisation and characterisation by the manufacturing process is more than additional but crucial. It is proposed to modify the text as follows:	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: The requirements regarding physico-chemical characterisation are the same for all IMPs ~~with additional~~ while for biological products more extensive biological characterisation is expected (see references). ~~of biological products.~~	
201-211	47	**Comments:** Should be more specific. Please clarify what is meant by biological characterisation and include in lines 212-213.	Partly accepted. Reference to IMP guidelines included in section 3.
214-218	13	**Comments:** It is unclear when a method for selecting a starting dose can be considered relevant, reliable and qualified. **Proposed change:** Please clarify or add cross reference.	Partly accepted. Reference to IMP guidelines included in section 3.
215-218	47	**Comments:** Could we define what a 'representative defined reference material' is?	Partly accepted. Reference to IMP guidelines included in section 3.
220	6	**Comments:** To emphasize the importance of qualification of the material, it would be beneficial to state the reason for the importance of qualification of the material, like it was stated in the previous version of this guideline. **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		In front of line 220, add: “During early development of a product, significant modifications to the manufacturing process frequently occur. It should therefore be ensured that the material used in non-clinical studies is representative of the material to be used…..”	
220-221	32	**Comments:** “Material” should clearly defined. **Proposed change:** The IMP batch(es) ~~material~~ used in non-clinical studies should be representative of the batch(es) ~~material~~ to be used for FIH/early CT administration.	Not accepted.
220-225	10	**Comments:** To this section, a sentence on changes and modifications of the manufacturing process should be added following line 225. **Proposed change:** “Any changes or modifications in the manufacturing process of the active substance during the non-clinical and early phase clinical development programme which might interfere with product heterogeneity, degradation profile or process-related impurities should be addressed. There should be sufficient assurance that product differences, should they occur, would not have an adverse impact on characteristics of the product, especially safety. The necessity of additional non-clinical bridging studies should be discussed based on adequate risk assessment.”	Partly accepted. Text amended.
220-225	33	**Comments:** To this section, a sentence on changes and modifications of the manufacturing process should be added following line 225.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
220-225	47	**Comments:** It is recommended that the types of studies with this requirement be limited to those for safety assessment. Note that early discovery phase studies cannot be practically conducted with FIH material as process chemistry/manufacturing will not have been fully defined at these stages. The stability of the active ingredient as well as of the formulation might be mentioned (e.g., precipitation or oxidation) **Proposed change:** "The material used ~~in non-clinical studies~~ in ***pivotal non-clinical safety studies*** should be representative of the material to be used for FIH/early CT administration."	Accepted. Text amended.
223	32	**Comments:** Product-related impurities could be added, as they might not be identical to degradation profile. **Proposed change:** A characterisation of the product including its heterogeneity, degradation profile, product- and process-related impurities should be performed.	Accepted. Text amended.
223-225	47	**Comments:** Re: "Special consideration should be given to the suitability and qualification of methods to sufficiently characterise the active substance and drug product." Particular attention is warranted if the formulation contains ingredients not described in the pharmacopeia. **Proposed change:** Add after line 225: Particular attention is warranted if the formulation contains ingredients not described in the pharmacopeia.	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
225	47	**Comments:** Include biologicals **Proposed change:** Special consideration should be given to the suitability and qualification of methods to sufficiently characterise the active substance and drug **or biological** product."	Partly accepted. Text amended.
225	51	**Comments:** BIO suggests including biological products in this bullet. **Proposed change:** Special consideration should be given to the suitability and qualification of methods to sufficiently characterise the active substance and drug or biological product.	Partly accepted. Text amended.
226-231	47	**Comment 1:** Although it is probably "implied" by use of the word "suitable", please reword to "suitable to provide the intended dose". **Comment 2:** Recommend that a reference be provided for formulation requirements and deleting the details from this section. There are formulation development requirements in this section that seem out of scope for this guidance. In specific response to Line 227, "Applicants should demonstrate that the intended formulation of the doses is suitable **to provide the intended dose per the appropriate guidance (reference here).**"	Partly accepted. Text amended.
227	20	**Comments:** It is not clear what is meant by "intended formulation of the doses".	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "intended final product to be dosed"	
227	46	**Comments:** "suitable" is too vague, it should be clarified from which perspective.	Partly accepted. Text amended.
230-231	20	**Comments:** "Compatibility of the product with primary packaging materials" is a CMC issue and should therefore reference existing guidance in this area. **Proposed change:** Please re-word, referencing CMC guidance.	Partly accepted. Text amended.
230-231	47	**Comments:** The sentence "the compatibility of the product with primary packaging materials and administration systems should be discussed" is considered to potentially widen the expectation on this matter. Other EU guidance (on primary plastic packaging evaluation) suggests such evaluation can be RISK BASED, with some product types not needing any evaluation. **Proposed change:** We would recommend aligning the content of this section 5.3 with the extant guidance – for example, changing the text to read "the compatibility of ~~the product~~ **some product types (e.g. solution products)** with the primary packaging materials and administration systems should be discussed."	Partly accepted. Text amended.
227-231	48	**Comments:** We note the requirement for compatibility testing with administration apparatus; however compatibility with diluents	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		should also be mentioned. Elements such as loss of drug associated with dilution, absorption to filters, IV set, syringes etc. would warrant consideration. At a minimum, the guideline should consider the need to confirm concentration/target mass will be delivered and that potency has not diminished. In addition, demonstrating that the assays to be used for concentration determination of the diluted dosing solution are suitable for the intended purpose and are accurate is also warranted. This is not clearly mentioned in the document. **Proposed change:** Applicants should demonstrate that the intended formulation of the doses is suitable. There is a risk of reduced accuracy in cases where the medicinal product needs to be diluted, to prepare very small doses, or the product is provided at very low concentrations as the product could be adsorbed to the wall of the container or infusion system**. Assays used to determine concentration of the drug product and diluted drug product should be accurate and fit for purpose.** The compatibility of the product with primary packaging materials and administration systems should be discussed. **Compatibility with diluent and administration apparatus should also be considered with a view to confirming concentration/target mass will be delivered and that potency has not diminished.**	
231	32	**Comments:** Mere discussion of the compatibility of the product with 1° packaging and administration system is not useful. Thus, “discussed” should be replaced by “evaluated”. **Proposed change:** (…)administration systems should be evaluated ~~discussed~~.	Partly accepted. Text amended.
233-234	20	**Comments:** It is not clear where in the ICH E6 guidance on GCP that the quality and state-of-the-art format is described, especially with regards to the nonclinical documentation. The ICH E6 guidance states only the general contents to be included in the clinical protocol and the IB.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "The documents supporting the CT application provide a clear, concise, and thorough and integrated summary of relevant nonclinical data in order to allow a meaningful assessment of human safety."	
233-234	47	**Comments:** It is not clear where in the ICH E6 guidance on GCP that the quality and state-of-the-art format is described, especially with regards to the nonclinical documentation. The ICH E6 guidance states only the general contents to be included in the clinical protocol and the IB. **Proposed change:** This sentence should be deleted or changed to: "The documents supporting the CT application should provide a clear, concise, and thorough summary of relevant nonclinical data in order to allow a meaningful assessment of human safety."	Partly accepted. Text amended.
233-236	14	**Comments:** ICH E6(R2), as a primarily clinical guideline, is not an ideal reference for "state-of-the-art" regarding non-clinical work. **Proposed change:** Delete entire paragraph. Detailed requirement for data to be presented are listed in the following subparagraphs.	Partly accepted. Text amended.
234-236	10	**Comments:** A clarification regarding the required format for the different types of documents should be provided. It is currently not clear whether "GCP" refers to the IB and whether the intention is to use the CTD format for IBs in future. GCP requirements are rather unusual in the non-clinical context. **Proposed change:** "… thus providing adequate information on the performed non-clinical studies to <u>support</u> a meaningful <u>risk</u> assessment,	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		which should be provided as a discussion integrating the available evidence and arriving at clear conclusions, substantiating the basis for guidance of the investigator. In addition, the inclusion of a tabulated …"	
235-236	3	**Comments:** Strengthening is needed at 4.4 and in Section 6 (lines 235-236) in respect of the findings in non-clinical safety studies that are relevant when designing FIH/early CTs. Encouragement for the inclusion in protocol of "a tabulated summary containing an overview of all relevant non-clinical data" is insufficient. EMA Guidance should explicitly ensure that these findings are summarized quantitatively in the protocol. Please see RSS recommendations.	Partly accepted. Text amended.
235-236	12	"*The inclusion of a tabulated summary containing an overview of all relevant non-clinical data is encouraged*." (section "6. Non-clinical aspects") **Comments:** It is not clear: • the added value of a tabulated summary • the term "relevant" Emphasis should be given to provision of a well-integrated, thorough risk assessment which is more readily conveyed in textual format. **Proposed change:** This should be deleted ~~The inclusion of a tabulated summary containing an overview of all relevant non-clinical data is encouraged.~~	Partly accepted. Text amended.
235-236	20	**Comments:** We agree that the CTA filing should contain an integrated summary of all relevant nonclinical findings. However, we	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		believe that a tabular form should not be mandated and hence we ask that the agency redraft the section indicating the requirement for an integrated summary of the safety findings in the IB but not the format in which it should be provided. **Proposed change:** The inclusion of integrated summary containing an overview of all relevant non-clinical data is required in the IB.	
235-236	23	**Comments:** Suggestion to specify the location of the tabulated summary in the study documentation. **Proposed change:** The inclusion of a tabulated summary containing an overview of all relevant non-clinical data **in the IB or IMPD** is encouraged.	Partly accepted. Text amended.
235-236	28	**Comments:** We are highly supportive of recommendation to include a tabulated summary containing an overview of all relevant non-clinical data.	Partly accepted. Text amended.
235-236	47	**Comments:** The expectation to provide a tabulated summary containing an overview of all relevant non-clinical data needs further context. Expectations regarding the level of detail, need to include all or only pivotal studies, and how one would provide a justification for the FIH CT starting dose and maximum dose is not inherently obvious.	Partly accepted. Text amended.
235-236	49	**Comments:** We suggest wording needs to be strengthened in section 4.4 and section 6 (lines 235-236) where “the inclusion of a tabulated summary containing an overview of all relevant non-clinical data is encouraged”.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "the inclusion of a tabulated summary containing an overview of all relevant non-clinical data is mandatory".	
235-236, 256-257, 306-307, 331-332, 351-353, 382	47	**Comments:** In regard to demonstration of relevance of animal models within the IB ("The inclusion of a tabulated summary containing an overview of all relevant non-clinical data is encouraged." And "The scientific justification for the use of these animal models of disease to support safety should be provided") while the audience for the IB is primarily principal investigators, the IB is the authoritative summary of all pertinent data to support development of the compound, and cross-referencing from the IMPD (nonclinical) is allowed by guidance (Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial). This FIH guidance document should be clear that the IB may contain all such information and cross-referencing may be used where applicable. **Proposed changes:** examples only (not an exhaustive list): Line 235-236, "The inclusion of ~~a~~ tabulated summary containing an overview of all relevant non-clinical data is encouraged – **this may be via tabulated summaries of studies in the initial version of the IB."**	Partly accepted. Text amended.
237	47	**Comment 1:** It would be helpful to have some flexibility as some of the disease models and alternative tox. models may not be GLP-compliant. **Comment 2:** Proposed language states that PK and PD studies should be performed "in accordance with the principles of GLP". This statement is open to a broad range of interpretation. There is also language in ICH s7a that supports this.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "The sponsor should confirm that all pivotal non-clinical safety studies in support of the CT application are conducted in compliance with Good Laboratory Practice (GLP). All other studies (e.g. PK and PD***, disease models***) should be of high quality and ***if appropriate,*** consistent with the principles of GLP. **When studies are not conducted in compliance with GLP, study reconstruction should be ensured through adequate documentation of study conduct and archiving of data.** "	
237-238	20	**Comments:** It is not feasible in all instances for pivotal nonclinical studies to be performed in compliance with GLP, e.g. when the pivotal safety study is a disease model or where alternative toxicity model has been employed). **Proposed change:** The Sponsor should indicate whether pivotal nonclinical safety studies conducted in support of the CT application are conducted in compliance with Good Laboratory Practice (GLP). Rationale should be provided in instances where pivotal studies are not conducted to GLP. All other studies (e.g. PK and PD**,** diseases models) should be of high quality and if feasible**,** consistent with the principles of GLP. When studies are not conducted in compliance with GLP, study reconstruction should be ensured through adequate documentation of study conduct and archiving of data.	Partly accepted. Text amended.
237-238	23	**Comments:** Suggestion to specify the location of the GLP statement in the study documentation. **Proposed change:** The sponsor should confirm **in the IB or IMPD** that all pivotal non-clinical safety studies in support of the CT application are conducted in compliance with Good Laboratory Practice (GLP).	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
237-238	28	**Comments:** We agree with the principle, however in cases where the pivotal studies have to be run in specific animal model of the disease, GLP compliance may not always be possible. **Proposed changes:** The sponsor should confirm that all pivotal non-clinical safety studies in support of the CT application are conducted in compliance with Good Laboratory Practice (GLP). If it is not the case, for whatever reason, we recommend that the sponsor to discuss the GLP compliance with regulatory agencies prior to CTA/MAA submission.	Partly accepted. Text amended.
237-238	52	**Comments:** Concern that some agencies may misunderstand the meaning of 'should' and require pharmacology studies fall into GLP requirements, which could prove very difficult for sponsors. **Proposed change:** The sponsor should confirm that all pivotal non-clinical safety studies in support of the CT application are conducted in compliance with Good Laboratory Practice (GLP). All other studies (e.g. PK and PD) should be of high quality and consistent with the principles of GLP to the extent that is possible.	Partly accepted. Text amended.
237-239	42	**Comments:** Would not PK/PD studies be considered pivotal non-clinical studies? **Proposed change:** Define what is considered as "pivotal non-clinical studies."	Not accepted. Term is widely understood.
237-239	51	**Comments:** Some of these disease models and alternative toxicology models may not be GLP-compliant. Additionally, it may be useful	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		to reference ICH M3(R2) & S6(R1) in Section 6.1 as they cover alternative models. **Proposed change:** The sponsor should confirm that all pivotal non-clinical safety studies in support of the CT application are conducted in compliance with Good Laboratory Practice (GLP). All other studies (e.g. PK and PD**,** diseases models) should be of high quality and consistent with the principles of GLP.	
238	20	**Proposed changes:** Insert “regulations” after GLP	Not accepted.
238-239	22	**Comments:** The reference to GLP suggests a limited understanding of GLP principles: Studies are either GLP compliant, or not with GLP only applicable to non-clinical health and environmental safety studies (Directive 2004/10/EC §2.1). “All other studies (e.g. PK and PD) should be of high quality **and consistent with the principles of GLP.”** **Proposed change:** Delete bold underlined part.	Partly accepted. Text amended.
239	9	**Comments:** For clinical lab expectations would it not be better to refer to GcLP rather than GLP?	Not accepted.
240	31	**Comments:** We fully support this statement. However, please provide guidance on regulatory acceptance for such 3R investigations.	Not accepted. Outside scope of the current document.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
240	34	**Comments:** "3R" principle should be defined. **Proposed change:** 3Rs (Replace, Reduce, and/or Refine laboratory animal use)	Not accepted – reference to Directive 2010/63/EU.
240-242	46	**Comments:** Subject not relevant to the guideline which is not on non-clinical testings. Should be deleted.	Not accepted.
240-243	13	**Comments:** To prevent that this guideline is mistaken as imposing a need for animal studies for biosimilars a sentence could be added. **Proposed change:** Include after line 243: "*Biosimilar candidates contain a version of a well-known biological active substance. Proper analytical and in vitro characterisation would generally obviate the need for animal studies.*". For reference in section 3. the following guideline should be included: "*Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues* (EMEA/CHMP/BMWP/42832/2005 Rev1).".	Not accepted. Too specific detail.
240-243	47	**Comment 1:** This section comprises mainly broad, general statements, which are not particularly illuminating. It does not make clear what exactly is intended by the term "animal model" – does this refer primarily to species (as implied by lines 247-252), to animal models of human disease or to something else. An animal model might be very relevant in one respect (e.g.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		metabolic profile) but irrelevant in another (e.g. target homology or expression profile). For disease models, in many instances, there is no single animal model, which can recapitulate all aspects of the human disease. In reality, utilizing multiple models reflecting different aspects of the disease in question and of the IMP pharmacodynamics may be the only feasible path forward. Strongly recommend reducing and focussing the text on the aspects species, pharmacodynamic models and models of disease. **Comment 2:** While section 6.1 speaks about “demonstration of relevance of the animal model”; there is no section that describes how the “relevance of the in vitro model” should be documented. **Proposed change:** 1) add a sentence after line 243 to express: “**The relevance and limitations of all models used should be carefully considered and discussed fully in the supporting documents”.** 2) add a sub-section on “Demonstration of relevance of the in-vitro model”.	
242-243	47	**Comments:** Using in vitro studies should not be recommended just “whenever possible”, but when scientifically sound. **Proposed change:** The use of in vitro studies, including studies using human material, is encouraged whenever **scientifically relevant and sufficiently validated.**	Accepted. Text amended.
244	46	**Comments:** Title of section 6.2 should clarify explicitely that it is talking about "Efficacy Animal Model"	Not accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
244-284	12	**Comments:** The demonstration of the relevance of the animal model in this section is based on “on-target” toxicity considerations only, although the aim of nonclinical studies is to address on-target and off-target safety issues, consistent with ICH guidelines. This is particularly important since off-target toxicities represent a large part of the toxicities identified in nonclinical studies with small molecules and they are very informative for the risk assessment in early clinical development. **Proposed changes**: Replace the section with: The demonstration of relevance of the animal model should follow the recommendations outlined in ICH M3(R2) and ICH S6(R1) guidances. The demonstration of relevance of the animal model(s) may include comparison with humans of: • if available, target expression, distribution, primary structure, and pharmacodynamic. It is recognised that these data are often not available in nonrodent species. • metabolism and other PK aspects **Justification:** • Line 252: The recommendation of tissue cross-reactivity (TCR) studies using animal tissues for monoclonal antibodies is **inconsistent with ICH S6(R1) guidance** which mentions that assessment of tissue cross reactivity in animal tissues is of limited value for species selection. A TCR study with a panel of human tissues only is recommended per ICH S6(R1) guidance. • Lines 256-257 (“*Therefore, in certain cases, studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals.*”): Animal models of disease may provide further insight	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		into the pharmacodynamic evaluation of a compound; However, as detailed in Morgan et al (2013) publication and **ICH S6(R1) guidance**, "targeted animal models are typically inappropriate to use in general toxicity studies…". "Instead, animal models should be utilized in a second or third tier approach to elucidate safety risks that were identified in the first trier of traditional nonclinical safety studies." The physiologic status of the disease animal models is not always representative of that in patients. In addition, in these models of disease, there is often a paucity of historical data for use as a reference when evaluating study results. • Lines 260-261: There are many cases for which the use of homologous proteins or of transgenic or humanised animals expressing the human target is not appropriate, i.e interaction of IMP with the humanised receptor in transgenic animals may not have similar physiological consequences to those in humans, and production process, range of impurities, PK and PD effects may differ between homologous form and the IMP intended for clinical use. **Proposed change:** "*Where no relevant species exists, the use of homologous proteins or the use of relevant transgenic or humanised animals expressing the human target* ***e****~~should be~~ considered.*" • Lines 266-270 (*"Qualitative and quantitative differences may exist in biological responses to a new IMP in animals compared to humans(…)"*): Because qualitative and quantitative differences generally exist in biological and toxicological responses to a new IMP in animals compared to humans, **ICH M3(R2) guidance** recommends the use of 2 species (one non-rodent) in the toxicology studies with small molecules. • Lines 271-279 (*"Where there is evidence of species-specificity of action from in vitro studies with human cells compared with cells from a test species, the value of the in vivo response of the test species may be significantly reduced in terms of predicting the in vivo human response(…)"*): Although nonclinical studies with highly human-specific medicinal products may not reproduce the intended human pharmacological effect in animals, and may give rise to misinterpretation in PD effects, they can address "off-target" unexpected toxicities which represent a large part of the toxicities identified in nonclinical safety studies with small	

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		molecules. It should be clarified what the human-specific medicinal products are in the guidance.	
244-284	50	Increased emphasis on nonclinical models to effectively predict the target therapeutic dose range: **Comments:** Given the broad nature of the guidance it must be recognized that the quantitative ability of non-clinical pharmacological models varies widely across therapeutic areas and likely even across targets within therapeutic areas. Consequently the absolute quality of submissions, ability to evaluate and relative subject safety will vary similarly. When the species used for pharmacological models differ from those used in toxicology studies, the ability to define pharmacological activity and safety in the same species and thereby derive a therapeutic ratio may be challenging. There are uncertainties and unknowns about translation of non-clinical models to human disease **Proposed change:** Acknowledge that although nonclinical models can provide a scientific basis for predicting the efficacious exposure range, they cannot definitively predict the therapeutic exposure. Therefore, they should be used as a tool to guide dosing rather than an absolute limit on early phase studies. Clinical experience obtained later in development will ultimately define the therapeutic range. Lines 244-246: **"**The search for a relevant animal model should be documented and the model selected should be 246 justified in the Investigator's Brochure (IB). ***The relative strengths and limitations of the animal model(s) should be described."*** Lines 263-265: "The use of in vitro human cell systems could 264 provide relevant additional information, especially for the translation of the mode of action from animal 265 to human. ***Sponsors are encouraged to use human tissues or human cells as a component of nonclinical safety evaluation where possible and when appropriate in order to help de-risk human specific toxicities or predict human-specific effects."***	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
245	30	**Comments:** This information should also be summarised in the protocol. **Proposed change:** The search for a relevant animal model should be documented, and the model selected justified, in the Investigator's Brochure (IB) and summarised in the Protocol.	Partly accepted. Text amended.
245-246	12	"*The search for a relevant animal model should be documented and the model selected should be 245 justified in the Investigator's Brochure (IB).*" (Section "6.1. Demonstration of relevance of the animal model") **Comments:** Although the relevance of the animal model should be justified in the IB, the added value to document the "search for a relevant animal model" and extent to which this "search" is needed is not clear. This may lead to unnecessary use of animals inconsistent with 3Rs. **Proposed change:** ~~The search for a relevant animal model should be documented and~~ **Tthe relevance of the animal** model selected should be justified in the Investigator's Brochure (IB).	Partly accepted. Text amended.
245-246	20	**Comments:** Although the relevance of the animal model should be justified in the IB, the added value to document the "search for a relevant animal model" and extent to which this "search" is needed is not clear. This may lead to unnecessary use of animals inconsistent with 3Rs.	Partly accepted. Text amended.
245-246	47	**Comments:** It is recommended that this statement be revised to accentuate the initial version of the IB. As product development	Partly accepted. Text amended.

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		matures, this information may be considered non-informative to the PI (the primary audience of the IB) and as a consequence, Sponsors may delete this information from later iterations of the IB. **Proposed change:** "The search for a relevant animal model should be documented and the model selected should be justified **with**in the **initial** Investigator's Brochure (IB)."	
246	32	**Comments:** Both pro's and con's/limitations of the model should be described. Therefore, additional text proposed. **Proposed change:** (…) Investigator's Brochure (IB). The justification should be based on the aspects which indicate the similarity to/relevance for humans, but the limitations of the respective animal model should also be clearly described.	Partly accepted. Text amended.
247	32	**Comments:** Change was introduced to avoid any impression that comparison should be done with human/clinical data. **Proposed change:** (…) include comparison with the situation in humans of:	Not accepted.
247-252	47	**Comment 1:** In addition to expression, distribution, and primary structure any known differential biological effects of the target across species should be included. Percent protein binding can be of importance when considering the relevance of an animal model, particularly if it is highly protein bound **Comment 2:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		The suggestion that tissue cross-reactivity studies may be used to justify the relevance of the animal models appears to be in conflict with ICH S6(R1) guidance, which states that “Assessment of tissue cross reactivity in animal tissues is of limited value for species selection” Proposed change: “The demonstration of relevance of the animal model(s) may include comparison with humans of: • target expression, distribution and primary structure. However, a high degree of homology does not necessarily imply comparable effects **or safety findings**; • pharmacodynamics; • metabolism and other PK aspects; ***protein binding*** • r*eplace line 252 with:* ***target binding affinities and receptor/ligand occupancy and kinetics***	
247-252	51	**Comments:** The use of tissue cross reactivity studies with human and animal tissues (*e.g.,* mAbs) is advocated by the draft guideline. Considering the challenges of the immunohistochemistry (IHC) method (some mAbs are not good IHC reagents, lack of adequate positive control, low sensitivity), would a weight of evidence approach for off-target binding be more suitable which could cover both in silico analysis of the target expression (mRNA, protein) in tissues and homology of the target with other human proteins, as well as other techniques such as mammalian cell surface display, other human protein arrays, ISH, ISPCR etc., lack of off-target toxicity in GLP toxicology studies, other literature data. Additionally, there is no mention of what constitutes a relevant species with regards to relative potency to humans (*e.g.,* within 10-fold of the EC50/IC50 in humans). For mAbs, a relevant species is usually defined as one in which we are able mimic the type and duration of pharmacological activity as that intended in humans. Hence even if there is a 50-fold drop in potency to human, as long as we know we can dose high enough to achieve full human relevant pharmacology (with an additional exposure margin to assess off-target effects), then the species would still be relevant.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: The demonstration of relevance of the animal model(s) may include comparison with humans of: • target expression, distribution and primary structure. However, a high degree of homology does not necessarily imply comparable effects; • pharmacodynamics; • metabolism and other PK aspects; • on and off-target binding in tissue cross-reactivity studies or cell and protein arrays using human and animal tissues/cells/ proteins (e.g., for monoclonal antibodies).	
251	20	**Comments:** In demonstrating relevance of animal models for FIH CT it seems odd to include metabolism as a defining factor. At this point available information is mostly from in vitro systems and the prediction stemming from these assays is not strong valuable for species selection. It can be later in the development timeline but for FIH studies the value seems limited. In projecting human doses and dose escalation PK modeling can be used to good effect but this is mostly reliant on prediction of clearance, t1/2 and volume of distribution. Percent protein binding can be of importance when considering the relevance of an animal model, particularly if it is highly protein bound.	Partly accepted. Text amended.
252	20	**Comments:** The suggestion that tissue cross-reactivity studies may be used to justify the relevance of the animal models appears to be in conflict with ICH S6(R1) and Q&A guidance, which states that “Assessment of tissue cross reactivity in animal tissues is of limited value for species selection.” We recommend replacing this line with the following bullets:	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "The demonstration of relevance of the animal model(s) may include comparison with humans of: • target expression, distribution and primary structure. However, a high degree of homology does not necessarily imply comparable effects or safety findings; • pharmacodynamics; • metabolism and other PK aspects; protein binding • replace line 252 with: target binding affinities, receptor/ligand occupancy and kinetics and functional activity in species-specific cell-based systems	
252	32	**Comments:** It is proposed to delete the text. As stated in ICH S6(R1) "assessment of tissue cross reactivity in animal tissues is of limited value for species selection." **Proposed change:** ~~tissue cross reactivity studies using human and animal tissues (e.g. monoclonal antibodies).~~	Accepted. Text deleted.
252	34	**Comments:** Inconsistent with ICH S6(R1), which states that TCR in animal models is of limited value for species selection. **Proposed change:** We suggest referring to ICHS6(R1) for the use of TCR in animal model selection.	Partly accepted. Text amended.
252-284	30	**Comments:** Much of the discussion is relevant to biologicals rather than small molecules. Separate subsections for NBEs and NCE may	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		be useful.	
253-258	10	**Comments:** The focus of this paragraph is on the suggestion of an additional testing approach which may be considered in exceptional circumstances. This part appears to interfere with the reasoning regarding the use of relevant species in traditional toxicological studies. **Proposed change:** It is proposed to move this paragraph to the end of this section.	Partly accepted. Text amended.
253-258	47	**Comment 1:** The aims of studies addressing pharmacological activity and those addressing toxicology are somewhat opposed. While tolerability information may be obtained from pharmacological studies in a general sense the linking in this section is largely hypothetical. **Comment 2:** While reading it is not clear that this is a specific guidance for tox. We propose to provide at least guidance on the default choice of animal species for tox, and not only the hypothetical deviations/ exemptions. **Proposed change:** Insert at front of line 253. **In principle, the animal toxicity studies to initiate human clinical trials should be conducted in two mammalian species (one non-rodent) in accordance with ICH M3, ICH S6. For small molecule entities, at least one species (rodent or non-rodent) will be "pharmacologically" relevant, where both the presence of the target and the relative potency of the molecule against the target in the species used for toxicity studies and the intended patient population should be considered. As the animal doses in toxicity studies are generally far higher than the estimated human dose, complete pharmacological effects**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		can still be achieved in animals despite the difference in affinity. Both species should be relevant with adequate exposure and metabolism to assess the chemical toxicity" **For biotechnology-derived products, the selection of a single species is justified, in case there is only one pharmacologically relevant species for the clinical candidate.** Line 259 then starts here	
253 ff	31	**Comments:** Proposal: change of sequence: The search for the relevant model should be documented, the outcome justified. Based on the points mentioned in 247 ff and the available information first the typical toxicological species would be rated (relevant, not relevant), then in case of no relevant species, the alternative (e.g. homologous protein, disease model) should be discussed).	Partly accepted. Text amended.
256	9	**Comments:** Certain cases: do these apply to first in patient studies?	Accepted – yes.
256	47	**Comments:** Regarding "certain cases", Please clarify to what cases this applies?	Accepted. Text amended.
256-257	20	**Comments:** "*Therefore, in certain cases, studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals.*" Apart from the question whether or not this type of studies would allow for a sufficient high/frequent dosing schedule, depending on the type of molecule this may or not be aligned with ICH guidelines. The above cited lines 256-257 seems to be more appropriate for biologicals (ICH S6). However, if also considered applicable for small molecules this at least should fulfil requirements for conventional toxicity studies as defined in ICH M3 (re duration and 2 species requirements).	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
256-257	22	**Comments:** This paragraph contains rather speculative notions. “Animal models of disease that are thought to be similar to the human disease may provide further insight into pharmacological action and PK (e.g. disease-related expression of the target) **as well as dosing in patients and safety (e.g. evaluation of undesirable promotion of disease progression). Therefore, in certain cases, studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals. The scientific justification for the use of these animal models of disease to support safety should be provided.”** While it’s agreed that disease models may be of value to study pharmacology and – possibly – PK, there is little evidence that disease models in animals are suitable for safety studies to replace regular toxicity and safety pharmacology studies (lack of standardisation of physiological state; lack of background normal data; other…). Unless compelling evidence to the contrary is provided by SWP, it is suggested that scientific guidance and advice from Regulatory authorities would be required if safety assessment in disease models is planned as a substitute for the standard safety studies. **Proposed change:** Re-phrase yellowed part or delete section “In case studies performed in animal models of disease are contemplated as an acceptable alternative to toxicity studies in normal animals, applicants are advised to seek scientific advice.”	Partly accepted. Request is for a supportive scientific rationale from whatever source.
257	31	**Comments:** Regarding the use of disease models in safety testing, sufficient background information should be available (provided with the justification) to allow a thorough assessment of the observations/ findings.	Accepted.
259	3	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Welcome is the statement (line 259) that: “Non-clinical studies in non-relevant species may give rise to misinterpretation and are discouraged”.	Text amended.
259	5	**Comments:** Line 259 is in itself irrelevant.	Partly accepted. Text amended.
259	20	**Comments:** Line 259: “*Non-clinical studies in non-relevant species may give rise to misinterpretation and are discouraged.*” This may be more appropriate for biologicals where single species testing is foreseen. However, for small molecules there is the requirement within ICH M3 to perform studies in 2 species (rodent and non-rodent) regardless of PD activity, in order to detect off-target toxicities. The proposed revision is not consistent with ICH M3 and should be revised.	Partly accepted. Text amended.
259	31	**Comments:** The concept is in general supported, however off- target information (mentioned in lines 160, 200, 614) may be obtained from non relevant species. In case the options given in lines 260/261 are not possible-considering also the comment in lines 261-263, no animal testing would be required; consequently, no information on “on” and “off target” toxicity is available.	Partly accepted. Text amended.
259	50	**Comments:** Clarification is requested in regards to how the Sponsor may determine what is a “relevant” species and what is a “non-relevant” species. This statement should be revised to reflect that the fact that it is common for toxicology programs to utilize 2 different species and 1 of the 2 species may be more “relevant” or only 1 of the 2 species may be classified as “relevant” according to this guidance. If “relevance” is based on pharmacodynamics, clarification is needed on the need for 2 species if 1 is “non-relevant” from a PD perspective to examine potential off-target, chemical-related toxicities of small molecules.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
259-261	26	**Comments:** It is unclear whether the guidance is advocating the use of transgenic animals or homologous proteins in non-clinical safety studies generally or in pharmacodynamic models alone. ACRO notes that, if the former, interpretation of toxicological outcomes is very complex due to the sparsity of background data and the inherently uncharacterised nature of these models with respect to nonclinical safety endpoints; also, creation of homologous proteins may have unintended and uncharacterised “off target” interactions, not present in the actual drug substance being developed. ACRO therefore recommends that the scope of this discussion is clarified and, if it relates to non-clinical safety studies in general, that these comments about the difficulty of their interpretation are included in the guideline. **Proposed change:** Add a statement to clarify the scope of the discussion of the use of transgenic animals or homologous proteins and, if the scope includes non-clinical safety studies, add comments about the difficulty of their interpretation.	Partly accepted. Text amended.
259-265	6	**Comments:** Non-clinical studies in non-relevant species are discouraged. Does this apply to pivotal nonclinical safety studies? So in essence, similar to ICH S6(R1), could a one-species strategy be acceptable also for non-biologics if only one species is relevant?	Partly accepted. Text amended.
260	32	**Comments:** It is not clear why the concept for a “homologous drug” should be limited to proteins. Please change “homologous proteins” to “homologous molecules”. **Proposed change:** (…) homologous ~~proteins~~ molecules or the use (…)	Not accepted.
260-	34	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
261		Consider clarifying the use of transgenic animals in combination with WT animals for appropriate interpretation. Use of transgenic or humanized animals can provide a great deal of pharmacologic and toxicological information when considering relevant species. It is also important to be able to interpret the data which needs extensive natural history studies of the animal model to be able to statistically associate an effect to a molecule and not to a long term effect of a genetic modification.	Text amended.
260-261	47	**Comments:** There is lack of details in the guidance as to the specific requirement of the tox package when using homologous proteins or TG/humanized animals. For example, what is the basic information to be generated and do these studies need to be in GLP?	Not accepted. Too specific detail.
262	32	**Comments:** More stringent wording is proposed. **Proposed change:** (…) these models ~~might be more~~ are only informative (…)	Partly accepted. Text amended.
263	46	**Comments:** suggest amending "in vitro" to "in vitro/ex vivo" **Proposed change (if any)** see above.	Not accepted.
266-270	51	**Comments:** BIO suggests deleting this paragraph which does not add any specific additional information.	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: ~~When planning FIH/early CTs, sponsors and investigators should identify the potential factors of risk and apply appropriate risk mitigation strategies. These factors should be addressed appropriately for all FIH/early CTs in the sponsor's CTA.~~	
271-275	6	**Comments:** It is stated that where there is evidence of species-specificity of action from in vitro studies with human cells compared with cells from a test species, the values of the in vivo response of the test species may be significantly reduced… Is qualification/validation of assay for the in vitro human cell assays required? If yes, this should be added.	Partly accepted. Text amended.
276-281	20	**Comments:** In the case of protein therapeutics, a potential 4th issue is the inability to obtain sufficient exposures in the animal model in the case of high immunogenicity. **Proposed change:** line 278 "give rise to misinterpretation of PK and PD results, including potential exposure limitations"	Partly accepted. Text amended.
276-281	47	**Comments:** In the case of highly human-specific medicinal products, the "misinformation" generated in the non-clinical studies should be balanced against the potential highly specific targeting that may occur (eg especially for antagonistic monoclonal antibodies). **Proposed change:** line 281"… and in vitro studies into the decision making process, **recognizing that highly human-specific medicinal products may also have highly specific modes of action".**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
276-281	47	**Comments:** In the case of protein therapeutics, a potential 4th issue is the inability to obtain sufficient exposures in the animal model in the case of high immunogenicity. **Proposed change:** line 278 “give rise to misinterpretation of PK and PD results**, including potential exposure limitations”**	Partly accepted. Text amended.
280-281	3	**Comments:** Welcome also is the statement (lines 280-281): “A weight-of-evidence approach should involve integration of information from in vivo, ex vivo and in vitro studies into the decision-making process.” See also RSS recommendations.	Partly accepted. Text amended and the concenpt of an uncertainty based approach has been introduced throughout the guideline.
280-281	28	**Comments:** Some clarity should be added regarding the weight of evidence approach by quoting guidance WC500139748 **Proposed changes:** A weight-of-evidence approach should involve integration of information from in vivo, ex vivo and in vitro studies into the decision-making process. More details for this kind of approach can be found in the “guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products”	Partly accepted. Text amended and the concept of an uncertainty based approach has been introduced throughout the

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			guideline.
282-284	20	**Comments:** "High human-specificity of a medicinal product makes the non-clinical evaluation of the risk to humans more difficult, but does not imply that there is always an increased risk in FIH/early CTs. However, in these cases, a proper discussion of the potential risks should be given to justify the conduct of a CT." Again this seems to be more appropriate for biologicals and how have a proper discussion on the potential risks when dealing with a novel target?	Not accepted. This is also relevant for chemical which have little or no affinity for animal targets.
282-284	47	**Comments:** This statement seems to confuse the concepts of specificity and affinity. However, the animal doses are often far higher than the human dose and consequently complete suppression of the target can be achieved in animals despite the difference in affinity. **Proposed change:** **If the therapeutic has higher affinity for the human target compared to the target in the toxicology species, this may make** the non-clinical evaluation of the risk to humans more difficult, but does not imply that there is always an increased risk in FIH/early CTs. However, in these cases, a proper discussion of the potential risks should be given to justify the conduct of a CT.	Not accepted.
282-284	51	**Comments:** This statement seems to confuse the concepts of specificity and affinity. However, the animal doses are often far higher than the human dose and consequently complete suppression of the target can be achieved in animals despite the difference in affinity. **Proposed change:**	Not accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		If the therapeutic has higher affinity for the human target compared to the target in the toxicology species, this may make ~~High human specificity of a medicinal product makes~~ the non-clinical evaluation of the risk to humans more difficult, but does not imply that there is always an increased risk in FIH/early CTs. However, in these cases, a proper discussion of the potential risks should be given to justify the conduct of a CT.	
283	32	**Comments:** The risk in a FIH study surely is increased when non-clinical data are non-conclusive or 'difficult'. Please modify the text as proposed. **Proposed change:** (…) but does not imply that there is ~~always~~ an ~~increased~~ unacceptable risk in FIH/early CTs.	Not accepted.
285	20	**Comments:** The "Pharmacodynamics" section should reference back to the Mode of Action discussion in Section 4.1 which discusses "High risk" pharmacodynamic effects, antagonist. vs agonist, the shape of the dose response curve etc. **Proposed change:** Primary PD studies should address the mode of action related to therapeutic use and provide knowledge on the interaction of the IMP with the intended target as well as with related targets (see Section 4.1).	Partly accepted. Text amended.
285	46	**Comments:** For a small molecule, the wording refers to the parent molecule. Would this section also applies to a situation where a significant metabolite is expected in human subjects? Will there be a need to partly characterize this metabolite prior to initiating the FIM study.	Not accepted. Too specific detail.
285	32	**Comments:**	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
ff		A statement should be added in section 6.2 of the guideline that the information on the pharmacodynamic studies (in vitro experiments as well as in vivo studies) provided with the CTA is sufficiently detailed to allow a thorough assessment. Thus, the applicant should information on experimental conditions/assay setups and should show the experimental results in Tables/Figures. Short verbal summaries are not considered sufficient.	detail.
285-287	47	**Comments:** It would be helpful for the "Pharmacodynamics" section to reference back to the Mode of Action discussion in Section 4.1 which discusses "High risk" pharmacodynamic effects, antagonist. vs agonist, the shape of the dose response curve etc. **Proposed change:** "Primary PD studies should address the mode of action related to therapeutic use and provide knowledge on the interaction of the IMP with the intended target as well as with related targets ***(see Section 4.1)***."	Partly accepted. Text amended.
286-287	51	**Comments:** The "Pharmacodynamics" section should reference back to the Mode of Action discussion in Section 4.1 which discusses "High risk" pharmacodynamic effects, antagonist versus agonist, the shape of the dose response curve etc. **Proposed change:** Primary PD studies should address the mode of action related to therapeutic use and provide knowledge on the interaction of the IMP with the intended target as well as with related targets (see Section 4.1).	Partly accepted. Text amended.
288-289	33	**Comments:** The effects (including off-target activities) of potential active metabolites are not considered. **Proposed change:** effects of the IMP and/or the potential active metabolites on other than…	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
288-289	47	**Proposed change:** "The selectivity and specificity of the IMP as well as secondary pharmacodynamics, defined as effects of the IMP on proteins other than the desired therapeutic targets, should be critically evaluated and documented." ~~"This might also include effects on other downstream or physiologically integrated endpoints"~~	Accepted. Text amended
288-289	51	**Proposed change:** The selectivity and specificity of the IMP as well as secondary pharmacodynamics, defined as effects of the IMP on proteins other than the desired therapeutic targets, should be critically evaluated and documented. ~~This might also include effects on other downstream or physiologically integrated endpoints.~~	Accepted. Text amended
291	30	**Comments:** Need to emphasise that both animal and human tissue non-clinical studies are required. **Proposed change:** The primary and secondary PD should be conducted in vitro, using both animal and human-derived material where feasible.	Not accepted.
291	47	**Comments:** Meaning of "material" could be clarified (drug vs. tissue) **Proposed change:** The primary and secondary PD should be conducted in vitro, using animal and human-derived ~~**material**~~ **tissue** and in vivo using animal models, as relevant.	Not accepted.
291-	51	**Comments:**	Not accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
292		BIO suggests that the tern “material” could be clarified (drug vs. tissue). **Proposed change:** The primary and secondary PD should be conducted in vitro, using animal and human-derived ~~material~~ tissue and in vivo using animal models, as relevant.	
292-295	22	**Comments:** What is the scientific evidence base that a routine requirement of studying physiological turnover of the target would materially aid/improve benefit/risk assessment? Such studies could be quite resource-demanding, and have no corresponding requirements in ICH guidances. “These studies should include target interactions preferably linked to functional response, e.g. receptor binding and occupancy, inhibition of enzymes, duration and (ir)reversibility of effect, dose-response relationships and **physiological turn-over of the target.”** **Proposed change:** Delete bold underlined part.	Partly accepted. Text amended to read ‘might’ instead of ‘should’.
292-295	47	**Comment 1:** A series of assays and studies are described, with the implication they should all be conducted. It is recommended to clarify that these are to be done when deemed relevant. **Comment 2:** typo: presented **Proposed change:** **Relevant studies can ~~These studies should~~** include target interactions preferably linked to functional response, e.g.	Partly accepted. Text amended to read ‘might’ instead of ‘should’.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		receptor binding and occupancy, inhibition of enzymes, duration and (ir)reversibility of effect, dose-response relationships and physiological turn-over of the target.	
292-295	51	**Comments:** A series of assays and studies are described, with the implication they should all be conducted. BIO recommends EMA clarify that these are to be done when deemed relevant. **Proposed change:** Relevant studies can ~~These studies should~~ include target interactions preferably linked to functional response, e.g. receptor binding and occupancy, inhibition of enzymes, duration and (ir)reversibility of effect, dose-response relationships and physiological turn-over of the target.	Partly accepted. Text amended to read 'might' instead of 'should'.
295	30	**Comments:** The animal and *ex vivo* human tissue PD data should be compared to better understand the usefulness of the selected animal species, as indicated by line 378 in Section 7.2. This can be added at the end of the paragraph. **Proposed change:** … target. The ex-vivo human PD data should be compared with animal data to illustrate the relevance of the selected non-clinical animal species to human pharmacology	Not accepted. Too specific detail.
296-297	47	**Comments:** This statement is unclear. Suggest modifying the text. **Proposed change:** ~~Data on the functionality of additional functional domains in animals, e.g. Fc receptor system for 296 monoclonal antibodies, should be present~~. **Where appropriate, data or information on target-unrelated effects, e.g. Fc-**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		mediated effects of monoclonal antibodies, should be provided.	
298-299	18	**Comments:** The requirement that a dose/concentration-response curve of the pharmacological effect(s) should be established with sufficient titration steps to detect significant pharmacological effects may be difficult for a first-in-human study where there are no clinical data and an animal model or PK/PD computerised model is not always available. **Proposed change:** From A dose/concentration-response curve of the pharmacological effect(s) should be established with sufficient titration steps to detect significant pharmacological effects. To A dose/concentration-response curve of the pharmacological effect(s) should be established with sufficient titration steps to detect significant pharmacological effects. For studies where it is not possible to provide these data, a suitable justification for their omission should be provided.	Partly accepted. Text amended.
298-299	52	**Comments:** Detecting significant pharmacology effects prior to FIH trials may be too restrictive. **Proposed change:** A dose/concentration-response curve of the pharmacological effect(s) should be established ~~with sufficient titration steps to detect significant pharmacological effects~~.	Partly accepted. Text amended.
300	20	**Comments:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		proposal for clarifying the goal of PKPD modelling. **Proposed change:** Suggesting removing “state of the art”. Suggested replacement “ A PKPD modelling approach is recommended that derives a mathematical relationship between the dose/concentration-response that can be applied to different clinical dosing scenarios (ie repeat dosing, different dose frequencies)"	
300	47	**Comments:** ”State-of-the-art” is subjective and not a useful term for general guidance. **Proposed change:** “**A scientifically-appropriate PK/PD** modelling approach is recommended…”	Partly accepted. Text amended.
300-301	9	**Comments:** PD and unwanted unblinding: Is Double Blind always required? define requirements.	Not accepted. Too specific detail.
300-301	12	“*A state-of-the-art PK/PD modelling approach is recommended, taking into consideration repeated dose applications as to be expected in the clinical situation.”* (Section “6.2. Pharmacodynamics”) **Comments:** We agree that PK/PD modeling projections can be valuable in many scenarios to formulate hypotheses in drug development. However, having this stated as a recommendation in a published guideline would be interpreted as if all submissions are expected to contain results of such modelling. This would add new expectations that exceed current ICH Guidance. **Proposed change:**	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		We suggest bringing for ICH negotiation the topic of when it may be appropriate to have the modelling projections included in a regulatory submission.	
300-301	16	**Comments:** Repeated dose is important, but also a wide range of dose amounts to identify the exposure-response relationship. Demonstration of the exposure-response relationship in the systemic circulation and in target organs in preclinical models should be encouraged.	Not accepted. Too specific detail.
301 & 353	13	**Comments:** Please, consider adding a reference to (draft) PBPK guideline.	Not accepted. Too specific detail.
302	30	**Comments:** This section should not include TK data. Mention of TK data should be moved to the toxicology section (6.5)	Partly accepted. Text amended.
302-310	39	**Comments:** (1) Protein binding (quantitative and qualitative) and Free fraction across species and human of the active moiety should be taken into consideration, for the interpretation of both PD and toxicity. (2) Data and information on active metabolite should be added with their off-target properties, including reversibility/ireversibility	Not accepted. Too specific detail.
303	52	**Comments:** The following nonclinical requirements for first in human or early clinical trials in orphan designations or accelerated situations may prove a large challenge. **Proposed change:**	Not accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		PK and toxicokinetic (TK) data, as per ICH S3, S6(R1), S9, M3(R2) and respective Q&A documents (if present), should be available in all species used for the non-clinical safety studies conducted and should adequately support the interpretation of data from in vivo PD models ~~before starting FIH/early CTs~~.	
303-307	12	"*Sponsors should supply a brief summary of the analytical assays used to characterise the non-clinical PK and TK, including their accuracy, precision and limits of quantification.*" (section "6.3. Pharmacokinetics) **Comments:** The added value of including a brief summary of the analytical assays, including their accuracy, precision and limit of quantification is not clear. Analytical assays included in GLP toxicity studies are validated according to Crystal City and draft FDA guideline recommendations and limit of quantification can be included in the tables summarizing the TK parameters in each study. **Proposed change:** ~~Sponsors should supply a brief summary of the analytical assays used to characterise the non-clinical PK and TK, including their accuracy, precision and limits of quantification..... and limits of quantification~~.	Not accepted. Required to support regulatory assessment.
303-307	16	**Comments:** The brief summary on analytical assays should be provided for each biological matrix evaluated (blood, plasma, urine, etc... as applicable). Also, encouragement of ultra-sensitive assays is encouraged to prevent BLQs in FIH studies.	Not accepted. Too specific detail.
303-307	20	**Comments:** The added value of including a brief summary of the analytical assays, including their accuracy, precision and limit of quantification is not clear. Analytical assays included in GLP toxicity studies are validated according to Crystal City and draft FDA guideline recommendations, and limit of quantification can be included in the tables summarizing the TK parameters in each study.	Not accepted. Required to support regulatory assessment.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
304-305	47	**Comments:** PK and TK data should not only be available from non-clinical "safety" studies, but in addition also from non-clinical "pharmacology" studies, given that systemic exposures at pharmacodynamically active doses in relevant animal models should be evaluated (line 308). **Proposed change:** Amend text to "…, should be available in all species used for the non-clinical safety **and pharmacology** studies conducted and should …"	Not accepted. Too specific detail.
305	13	**Comments:** It is not clear to what is referred to here. Does it concern an in vivo PK/PD model? **Proposed change:** Please clarify or add.	Partly accepted. Text amended.
306-307	50	**Comments:** A requirement to submit a brief summary of the analytical assays used to characterize the nonclinical PK and TK is more specific than what is outlined in ICH E6(R1) Good Clinical Practice; Section 7 "Investigator's Brochure". As Sponsors commonly cross-reference the IB within the Investigational Medicinal Product (IMPD) of Clinical Trial Applications, a blanket requirement for providing a description of assays and submitting assay data will result in excess and unnecessary detail being included in Investigators' Brochures. Furthermore, ICH guidance, i.e., ICH Q2(R1) already requires that such assays need to meet certain standards and be validated. **Proposed change:** ~~"Sponsors should supply a brief summary of the analytical assays used to characterise the non- clinical PK and TK, including their accuracy, precision and limits of quantification.~~ ***To provide reassurance with respect to the accuracy***	Not accepted. Required to support regulatory assessment.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		of the non-clinical exposure data and how this compares to that observed clinically, the sponsor may provide brief details of the analytical assays used for pharmacokinetic and/or toxicokinetic analyses together with the limits of sensitivity."	
308	20	**Proposed changes:** Revise to "Systemic and/or relevant local exposures…"	Not accepted. Too specific detail.
308-310	26	**Comments:** Toxicokinetics are relevant for all potential safety concerns, whether from primary pharmacodynamic or other toxicity findings. ACRO therefore recommends revising this sentence. **Proposed change:** Revise the sentence to read "Systemic exposures at pharmacodynamically active doses and toxic doses in the relevant animal models should be determined and considered."	Not accepted. Too specific detail.
308-310	33	**Comments:** The notions of protein binding, free fraction and active metabolites should be considered for the interpretation of PD and toxicity.	Not accepted. Too specific detail.
308-310	47	**Comments:** In addition to determining exposure levels of the parent at pharmacodynamically active doses, it is important to determine if there are biologically active metabolites in animals prior to FiH studies in humans. **Proposed change:** "Systemic exposures at pharmacodynamically active doses in relevant animal models **as well as the presence of**	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		biologically active metabolites should be determined …".	
310	47	**Comments:** The prediction of human exposure is completely missing here, at least a reference should be given to the human PK prediction, which is mentioned later (e.g. section 7.1), refer also to potentially expected differences e.g. accumulation in human or even induction	Not accepted. Too specific detail.
311	30	**Comments:** The importance of safety pharmacology should be stressed and data interpreted in terms of the margins of safety relative to the concentrations required for desired PD effects.	Not accepted.
311-322	16	**Comments:** Sections 6.4 or 6.5 should provide information on developmental toxicology or juvenile toxicology studies that might have relevance for pregnant women and children.	Not accepted. Too specific detail.
312	20	**Comments:** Regarding the availability of standard core battery data before the first administration in humans, it would be helpful to expand on the potential flexibility in certain circumstances, e.g. devastating rare diseases and devastating diseases with unmet medical need.	Not accepted. Too specific detail.
312-313	43	**Comments:** For oncology IMPs, standalone safety pharmacology studies are not required and the safety pharmacology parameters could be part of the GLP toxicology studies per ICH S9. **Proposed change:** "Safety pharmacology Standard core battery data should be available before the first administration in humans……"	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
314-316	26	**Comments:** The sentence includes the example of low selectivity of the IMP for its primary target, but it is not clear whether this relates to *in vitro* selectivity studies or observed *in vivo* toxicity (or both). For clarity, ACRO recommends an addition to the text. **Proposed change:** Revise the statement to read: "e.g. in case of low selectivity of the IMP for its primary target or limited margin between anticipated human exposure and significant toxicity."	Partly accepted. Text amended.
314-316	47	**Comment 1:** It is not clear why low selectivity alone of an IMP would be the reason to conduct additional safety pharmacology studies. In addition, there is no guidance on how to determine what studies would be selected. Even if selectivity is low, if affinity for secondary pharmacology targets is not high, there may be no reason to conduct stand-alone safety pharmacology studies if the endpoints of concern can be assessed in a toxicology study. **Comment 2:** "…e.g. in case of low selectivity of the IMP for its primary target." is insufficient. **Proposed change:** cause for concern, e.g. **substantial off-target pharmacology of the IMP, that cannot be assessed in toxicology studies or where potentially important off-target effects may be a consideration.**	Partly accepted. Text amended.
314-316	51	**Comments:** BIO finds this portion of the draft guideline text to be insufficient and unclear. As such, we suggest adding additional text. **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Additional studies to investigate effects in these and other organ systems should be conducted on a case-by-case basis where there is a cause for concern, e.g. in case of low selectivity of the IMP for its primary target**,** or where potentially important off-target effects may be a consideration.	
317	9	**Comments:** Do we need specific guidelines on the monoclonal antibody preclinical studies?	Not accepted. Too specific detail.
317	30	**Comments:** this section should include mention of TK data and of putative margins of safety for NOAEL and NOEL.	Not accepted. Too specific detail.
317	47	**Comments:** For section 6.5, do we need specific guidelines on the monoclonal antibody preclinical studies?	Not accepted. Too specific detail.
317	47	**Comments:** For Section 6.5. Some details should be added when biologics show immunogenicity related findings in animal tox species, more in particular how the situation should be handled and what information will be needed?	Not accepted. Too specific detail.
317-332	47	**Comments:** The guidance places a great deal of the justification of toxicology animal species relevance for small molecules on the intended target similarity to humans. While this is a fair concept, 1) it is out of alignment with ICH M3(R2) requirements for a rodent and non-rodent species. And 2) it diverts the focus to primary pharmacology at the expense of off-target surveillance. This latter point is particularly important because even when a sponsor conducts an extensive in vitro off-target battery, there still could be some significant off-target protein that mediates toxicity that may be best detected in vivo.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Determination of the mechanism of toxicity of target organs found in toxicity studies can be a lengthy process and may often be inconclusive. Further, determining the definitive cause of death in preclinical toxicity studies is not always possible, even when targeted studies for this purpose are conducted. Investigative studies for cause of death, mechanism of toxicity or obtaining a clinical biomarker to warn of a possible serious or life-threatening toxicity should be performed when the toxicity or mortality is of clinical relevance. Relevance would be determined by: 1) there is a modest or low exposure margin from the proposed clinical exposure range and the animal exposures where the serious toxicity or mortality is observed; 2) the sponsor is asserting that the animal toxicity is irrelevant to humans and wishes to dose humans to similar exposures – therefore studies showing that the mechanism of toxicity is animal specific would be warranted. However, when a serious or life-threatening toxicity is observed at very high doses/exposures in animal studies that far exceed the clinical range, then such follow up studies for cause of death or mechanism of toxicity are not necessary. **Proposed changes:** The following language should be added to the guidance in section 6.5 after line 319: **"For small molecule entities directed to a human target, at least one species (rodent or non-rodent) should be pharmacologically relevant, where both the availability of the target and the relative potency of the molecule against the target in the species used for toxicity studies and the intended patient population should be considered. Both species should be relevant with respect to adequate exposure and metabolism to assess the chemical toxicity. Metabolism similarity to humans can be covered by one of the 2 species or by both profiles when combined, but each species alone need not recapitulate human."** This wording is also consistent with ICH M3(R2). **Proposed changes:** The following language should replace lines 329-332 in the guidance in section 6.5 that begins with "If mortalities and/or serious…: **"When serious toxicity or mortality is observed non-clinically, these effects may require follow up studies to**	

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		determine cause of death or the mechanism of toxicity if this information is relevant to the clinical trial design or safety monitoring plan. This is usually driven by the exposures where the serious toxicity/mortality is observed. If these occur at exposures in far excess of the clinical range then cause of death or mechanism of action studies would not be required. Some mortalities/serious toxicities are poorly translated to humans, for example species-specific immune reactions with mAbs. These toxicities may be categorized as not clinically relevant with the appropriate data and/or rationale.	
318	47	The toxicology programme should be performed in relevant animal species (see section 6.1) and include TK as discussed in section 6.3. **Comments:** Definition of relevant species requires further clarification and needs to be consistent with existing ICH guidelines, in particular ICH M3. Animal species may lack the target but can be of relevance for a. secondary targets b. physicochemical conditions that trigger off target toxicity (e.g., liver based on covalent binding, phototoxicity, phospolipidosis, QT-prolongation, bone marrow toxicity, etc) Guidance needs to be aligned with ICH M3	Not accepted. Too specific detail.
320-321	14	**Comments:** “When factors influencing risk are identified […], the inclusion of additional endpoints to the toxicology studies should be considered.” The very purpose of the toxicology studies is to identify factors influencing risk, and this sentence is therefore incomprehensible. **Proposed change:**	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Reformulate or delete.	
322	47	**Comments:** "Toxicity can be results of exaggerated pharmacological actions. However, these types of effects should not be ignored when establishing a safe starting dose…." For certain types of drugs the exaggerated pharmacology cannot be avoided owing to use of healthy animals e.g. insulin and it should be possible to justify why the exaggerated pharmacology should not be used for establishing the safe starting dose. **Proposed change:** Suggest rephrasing "Toxicity can be the result of exaggerated pharmacological actions. While these types of effects should not be ignored when establishing a safe starting dose **based on NOAEL doses** it can be justified why these pharmacological effects are not of risk in the investigated **patient** population. The corresponding exposure will contribute to the determination of the dose…" …	Partly accepted. Text amended.
322-325	50	**Proposed change:** “However, these types of effects should not be ignored when establishing a safe starting dose for humans and the corresponding exposure will contribute to the determination of the dose escalation range**, *dose escalation steps and rate of progression*** to be investigated in humans. Primary and secondary PD can support the generation of mechanistic hypotheses regarding the toxicities seen in vivo and help in the interpretation of the human relevance of these findings.”	Partly accepted. Text amended.
322-325	14	**Comments:** “Toxicity can be the result of exaggerated pharmacological actions. However, these types of effects should not be ignored when establishing a safe starting dose for humans and the corresponding exposure will contribute to the determination of the dose escalation range to be investigated in humans.” This sentence is redundant since the purpose of toxicology is to characterise **all** adverse effects, whether target-related or	Not accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		not. **Proposed change:** Delete.	
327	26	**Comments:** ACRO recommends that the term "target organs" be defined. It is not clear whether this is dependent on the exposure associated with toxicity compared to the exposure expected in humans. If not, there will always be a target organ at sufficiently high doses. **Proposed change:** Define what is meant by “target organs in the non-clinical studies”.	Not accepted. Widely understood term.
327-328	10	**Comments:** It is rather the adverse effects at the target organs than the target organs themselves that may warrant particular monitoring in the clinical trials. **Proposed change:** “An evaluation as to whether the adverse effects identified in the non-clinical studies warrant particular monitoring in the CT should be undertaken.”	Not accepted. Widely understood term.
327-329	47	**Comments:** This should also address the availability of monitoring for any potential toxicities. There would be more concern over a toxicity, which could not be readily detected by clinical monitoring than one which is. **Proposed change:**	Not accepted. No need to state this.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		"An evaluation as to whether the target organs identified in the non-clinical studies warrant particular monitoring in the CT should be undertaken. Serious toxicity should lead to a more cautious approach when setting doses in the FIH/early CTs. ***Findings which are not amenable to clinical monitoring in these trials might be of greater concern than those that can be easily monitored and tracked (both onset and recovery)***. Proceed to the replacement text for the next line that starts "If mortalities…' as noted below under Line 329-332	
328	47	**Comments:** What is to be understood under "serious toxicity", can that be clarified?	Not accepted. Defined in line with ICH guidance.
328-329	10	**Comments:** The approach of a more integrated assessment should be strengthened here. The following sentence should be added in line 329. **Proposed change:** "Additional aspects for increasing concern should be taken into consideration as appropriate, including but not limited to steepness of dose-exposure and/or dose-toxicity responses, low safety margins, non-monitorable adverse effects, toxicity without pre-monitory signs, potentially irreversible findings, non-linear PK, inconsistent/variable pharmacodynamic responses and/or systemic exposures within or between animal species, etc. (see also sections 7.3 and 7.4 below)."	Partly accepted. Text amended.
328-329	33	**Comments:** The approach of a more integrated assessment should be strengthened here. The following sentence should be added in line 329. **Proposed change:** "Additional aspects for increasing concern should be taken into consideration as appropriate, including but not limited to	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		steepness of dose-exposure and/or dose-toxicity responses, low safety margins, non-monitorable adverse effects, toxicity without pre-monitory signs, potentially irreversible findings, non-linear PK, inconsistent/variable pharmacodynamic responses and/or systemic exposures within or between animal species, etc. (see also sections 7.3 and 7.4 below)."	
329-331	34	**Comments:** Mitigation of serious toxicity should be evaluated. Evidence of precursor serious toxicity should be addressed. **Proposed change:** If mortalities and/or serious toxicity are observed in non-clinical studies, an evaluation of putative mechanism and precursor of the serious event of toxicity and/or cause of death is expected (e.g. consideration of histopathological examination of deceased animals). Mitigation of such serious toxicity should be evaluated.	Partly accepted. Text amended.
329-332	3	**Comments:** Correctly, the EMA Guidance (lines 329-332) underscores that: "If mortalities and/or serious toxicity are observed in non-clinical studies, an evaluation of putative mechanism of toxicity and/or cause of death is expected to be addressed . . . ".	Partly accepted. Text amended.
329-332	20	**Comments:** Regarding determination of cause of death, this can be very difficult to assign with confidence, even when histopathology has been conducted. For the guidance, we believe a realistic expectation is that the sponsor state if the cause of death where it's clear and state that it could not be determined when it's not possible. Also, single dose escalation studies frequently have no histopathology assessments, but can induce mortality and for humane reasons, those lethal doses are not repeated in subsequent multi-dose toxicity studies. **Proposed change:** Please remove the words "an evaluation of the putative mechanism of toxicity" and replace with "If mortalities and/or serious toxicity are observed in non-clinical studies, assignment of the cause of death will be attempted and reported in	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		the CTA where the data indicate a clear cause of death. Consideration of histopathological examination of deceased animals, which is certainly necessary in pivotal studies, should also be considered for dose range finding studies where appropriate. When single dose toxicity studies are performed in recycled, colony animals (large animals), histology is not required as histologic effects from prior, unrelated IMP administrations may be present and confound the toxicity profile. In addition, determination of cause of death in satellite TK animals (rodents) is typically not required as the stress of anesthesia commonly induces unintended mortality that is not primarily IMP-related. Single dose escalations studies may induce mortality, but commonly do not have histology endpoints in the protocol. These lethal doses need not be repeated in repeat single dose studies with histology or subsequent multi-dose toxicity studies for humane reasons, especially when these mortalities are observed at large exposure multiples of the anticipated therapeutic exposure and repeat-dose toxicity studies define target organs at lower exposures than those inducing acute lethality.“	
329-332	27	**Comments:** Animal deaths are not uncommon in toxicology studies, especially in early dose-range finding studies. In many cases, it is not feasible to determine the exact mechanism leading to the deaths, and at most sponsors might be able to rule out certain mechanisms (i.e. histopathological findings in brain). **Proposed change:** If mortalities and/or serious toxicity are observed in non-clinical studies, a discussion of the potential mechanism of toxicity is expected (e.g. consideration of histopathological examination of deceased animals, which is certainly necessary in pivotal studies and should also be considered for dose range finding studies; assessment of whether mechanism is likely C_{max} or AUC-related).	Partly accepted. Text amended.
329-332	47	**Comment 1:** If animals were to have serious AEs after dosing with an IMP, and this toxicity was due to effects unlikely to translate	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		directly to humans, then it would not be necessary to take a more cautious approach to human dosing in this case. **Comment 2:** Determination of the mechanism of toxicity will vastly increase the number of toxicity studies needed for any given CTA. If several target organs are found then several experiments per target organ may be necessary. Determination of any mechanism of toxicity is a lengthy process that can take years and is often inconclusive. Regarding determination of cause of death, this can be very difficult to assign with confidence, even when histopathology has been conducted. For the guidance, a realistic expectation is that the sponsor state the cause of death where it's clear and that it could not be determined when it's not possible. Also, single dose escalation studies frequently have no histopathology assessments, but can induce mortality and for humane reasons those lethal doses are not repeated in subsequent multi-dose toxicity studies. When single dose toxicity studies are performed in recycled, colony animals (large animals), histology is not done and if it were, then histologic effects from prior, unrelated IMP administrations may be present and confound the toxicity profile. In addition, determination of cause of death in satellite TK animals (rodents) is typically not required as the stress of anaesthesia commonly induces unintended mortality that is not primarily IMP-related. If mortalities are observed in non-clinical studies, assignment of the cause of death will be attempted and reported in the CTA where the data indicate a clear cause of death, but can be reported as unkown when data do not support a clear conclusion. Determination of the mechanism of toxicity when mortality and/or serious toxicity is observed should be attempted if it brings useful information for setting clinical dose and/or monitoring of effects in the clinic (e.g. low therapeutic index to the toxicity). Endpoints can range from standard histopathology in pivotal and range finding studies when feasible - to separate, directed studies as required to underpin safe progression to CTs. **Proposed changes:** The following language should replace lines 329-332 in the guidance in section 6.5 that begins with "If mortalities and/or serious…: **"When serious toxicity or mortality is observed non-clinically, these effects may require follow up studies to**	

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		determine cause of death or the mechanism of toxicity if this information is relevant to the clinical trial design or safety monitoring plan. This is usually driven by the exposures where the serious toxicity/mortality is observed. If these occur at exposures in far excess of the clinical range then cause of death or mechanism of action studies would not be required. Some mortalities/serious toxicities are poorly translated to humans, for example species-specific immune reactions with mAbs. These toxicities may be categorized as not clinically relevant with the appropriate data and/or rationale.	
329-332	51	**Comments:** If animals were to have serious adverse events (AEs) after dosing with a mAb, and this was due to ADA, the approach to human dosing should be based upon the translatability of the finding. This will depend upon the nature of the IMP (human/humanized IgG mAb or Fab) and any potential role of the target in the proposed ADA-related mechanism of toxicity. As such, we suggest including assessment of translatability to the guideline. **Proposed change:** If mortalities and/or serious toxicity are observed in non-clinical studies, an evaluation of putative mechanism of toxicity and/or cause of death is expected to be addressed (e.g. consideration of histopathological examination of deceased animals, which is certainly necessary in pivotal studies and should also be considered for dose range finding studies). <u>The translatability of any mortalities/serious toxicities to humans should be assessed.</u>	Partly accepted. Text amended.
330-332	12	"*If mortalities and/or serious toxicity are observed in non-clinical studies, an evaluation of putative mechanism of toxicity and/or cause of death is expected to be addressed (e.g. consideration of histopathological examination of deceased animals, which is certainly necessary in pivotal studies and should also be considered for dose range finding studies)*" (Section "6.5. Toxicology") **Comments:** It should be recognized that the histopathological examination of deceased animals can fail to identify the cause of death,	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		especially if death is related to effects on cardiovascular, respiratory or neurological function.	
333-469	13	**Comments:** For section 7, it is proposed to further structure the information on healthy volunteers and patients. This as in the current draft the information on healthy volunteers is scattered throughout the sections and the information on patients is in one section. **Proposed changes:** We propose the following order: 7.1 General aspects 7.6 Route of administration 7.2 Starting Dose (including the first paragraph of 7.7 starting dose in patients) 7.3 Dose escalation 7.4 Maximal dose and dose range 7.5 Moving from single to multiple dosing 7.7 Addition information on patients that does not fit the other sections. We also propose to include a reminder that FIH and early clinical trials usually take place in healthy volunteers, and that patients are an exception.	Partly accepted. Text amended.
333-404	26	**Comments:** In section 7, PAD is used in some sentences, MABEL is used in others and some sentences use both terms. As PAD and MABEL both refer to the same concept (anticipated exposure/dose resulting in some pharmacological activity), ACRO	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		recommends the use of consistent terminology in order to avoid any potential confusion. **Proposed change:** Be consistent in use of PAD and/or MABEL.	
334	47	**Comments:** There should be differentiation between well-characterized and well-known targets and unknown targets	Not accepted. Too specific detail.
334-357	26	**Comments:** ACRO recommends including mention of pharmacokinetic factors that can have a significant effect on extrapolation of animal to human exposure, e.g. absorption (especially in compounds with low bioavailability), differences in significant routes of clearance, protein binding, etc. **Proposed change:** Including mention of pharmacokinetic factors that can have a significant effect on extrapolation of animal to human exposure.	Partly accepted. Text amended.
335-357	48	**Comments:** We acknowledge the general content of this section of the guideline is intended to ensure all available data are considered in determining starting doses and dose escalation in trial. We would however make the general comment that all components mentioned here may not apply in the context of biological IMPs where PK can be relatively predictable from preclinical studies.	General agreement.
336-337	5	**Comments:** vague language	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: a more general statement that clinical trials should be done in an efficient way with scientific substantiation	
337-338	20	**Comments:** The document talks about “rapid attainment of the trial objectives without exposing large numbers of subjects.” Could a line be added that addresses what is meant by “large number” or a reference to 8.2.5 that talks about size of cohorts?	Partly accepted. Text amended.
339-341	30	**Comments:** The use of all available data when making starting dose and dose escalation decisions is critical to the safe conduct of FIH studies. This section could be strengthened by replacement of ‘should’ with ‘must’. **Proposed change:** All available non-clinical information (PD, PK, TK and toxicological profiles, dose or exposure/effect relationships etc.) must be taken into consideration for the calculation of the starting dose, dose escalation steps and maximum dose.	Not accepted. Term ‘should’ is appropriate for a guideline.
339-341	33	**Comments:** maximal exposure can also be derived from all available non-clinical information. **Proposed change:** … dose escalation steps and maximum dose/exposure.	Partly accepted. Text amended.
339-341	39	**Comments:** Exposure missing **Proposed change:** All available non-clinical information (PD, PK, TK and toxicological profiles, dose or exposure/effect relationships, etc.)	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		should be taken into consideration for the calculation of the starting dose, dose escalation steps and maximum dose/exposure.	
339-344	12	**Comments:** "*All available non-clinical information (PD, PK, TK and toxicological profiles, dose or exposure/effect relationships, etc.) should be taken into consideration for the calculation of the starting dose, dose escalation steps and maximum dose. Furthermore, clinical data (e.g. PK, PD and reports of adverse events) emerging during the trial from previous dosed cohorts/individuals needs to be taken into account, in line with pre-specified decision criteria. Experience, both non-clinical and clinical, with molecules having a similar mode of action can also be useful*" (Section "7.1 General aspects") **Proposed change:** Because of limitations of translatability on nonclinical models to humans for many therapeutic areas, the guidance should accommodate exploratory clinical trials, as **outlined in ICHM3 (R2) guidance**, which allow earlier and more efficient clinical evaluation of PK, PD and other markers of target engagement.	Partly accepted. Reference is made to exploaratory clinical trials and ICH MS(R2) in section 7.1.
339-344	20	**Comments:** Because of limitations of translatability on nonclinical models to humans for many therapeutic areas, the guidance should accommodate exploratory clinical trials, as outlined in ICHM3 (R2) guidance, which allow earlier and more efficient clinical evaluation of PK, PD and other markers of target engagement.	Partly accepted. Reference is made to exploaratory clinical trials and ICH MS(R2) in section 7.1.
339-344	26	**Comments:** To ensure the reliability of information on which dose decisions are made, ACRO recommends that this paragraph should include a statement requiring decisions about starting dose, dose escalation steps and maximum dose to be based on	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		non-clinical and clinical information that has been subject to quality control. **Proposed change:** Include a statement requiring decisions about starting dose, dose escalation steps and maximum dose to be based on non-clinical and clinical information that has been subject to quality control.	
341-343	3	**Comments:** In the BIAL trial, the problem was that the pre-specified decision criteria (lines 341-343), as approved by ANSM (see Bird et al. in Pharmaceutical Statistics 2017: accepted), were per-cohort, not across-cohorts as the EMA Guidance rightly requires.	General agreement.
342	5	**Comments:** 'Clinical data needs to be taken into account'. In chapter 6 less restrictive wording is used (might/may etc.), while here it is stated that clinical data needs to be taken into account. **Proposed change:** Use more restrictive language in the entire document.	Partly accepted. Text amended where appropriate.
342	40	**Comments:** Should it be specified that the emerging data should be taken into account during dose escalation decisions. Currently it just says that it should be taken into account, but not what for.	Not accepted. Statement is referring to the preceding sentence.
342-344	20	**Comments:** The emerging clinical data may be unexpected / not predicted by the preclinical studies and so pre-specified criteria may not be possible in the protocol. The statement "in line with pre-specified decision criteria" could be removed or expanded	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		to ensure it is clear that the criteria may have been pre-specified in the protocol or at study level Safety Review Committees.	
343	20	**Comments:** This line refers to “pre-defined decision criteria” for the first time in the document without context. **Proposed change:** Consider referencing section 8.2.10 and/or add the following: “Decision criteria should be pre-defined to guide actions based on clinical data (…etc…) that emerges during the trial…”	Partly accepted. Text amended.
343-344	47	**Comments:** Internal experience or external (competitor) data for other IPA’s in same class may not be available or accessible in the absence of a global registry/database/website similar to clinicaltrials.gov. Off-target safety signals for other IMPs would not be relevant.	Not accepted. Too specific detail.
343-344	47	**Comments:** The definition of “mode of action” may be unclear. The intent is to enable the Sponsor to utilize data from other compounds that engage the same target in the same manner **Proposed change:** Experience, both non-clinical and clinical, with molecules **that bind to the target in the same manner** ~~**having a similar mode of action**~~ can also be useful.	Not accepted. Too specific detail.
343-344	51	**Comments:** The definition of “mode of action” may be unclear. The intent is to enable the Sponsor to utilize data from other compounds that engage the same target in the same manner.	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Experience, both non-clinical and clinical, with molecules that bind to the target in the same manner ~~having a similar mode of action~~ can also be useful.	
343-344, 677-681	50	**Comments:** External (competitor) data for other IMPs in same class may not be available or accessible in the absence of a global registry/database/website similar to clinicaltrials.gov Off-target safety signals for other IMPs would not be relevant.	Not accepted. Too specific detail.
345 & 400	9	**Comments:** Starting dose for FIH, subsequent doses will be determined based on available safety/PK data. Estimated dose levels can be chosen, however final dose levels will be based on interim analysis of available data. Leaving these dose levels flexible might avoid amendments. Maximum exposure can be defined as not to exceed.	Partly accepted. Text amended.
345-346	20	**Comments:** FIH is the "learning" phase of drug development; thus the protocol doses are not selected a priori to satisfy a predefined dose-exposure-response relationship. Therefore, other than the starting and maximum dose justification, requiring justification of exposure for the in-between dose level are not useful. Suggest only requiring exposure for the starting, maximum and any critical dose level of therapeutic relevance, if known.	Partly accepted. Text amended.
345-346 & 351-353	3	**Comments:** Particularly welcome is the clear statement (lines 345-346) that: "The starting dose and estimated exposure levels chosen for all cohorts and study parts should be pre-specified and a justification for these steps should be outlined in the study protocol". The methods used and calculations on how doses and estimated exposure levels were determined, including methods for modelling, should be included in the IB and summarised in the protocol (lines 351-353).	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Summarization in the protocol is essential to meet RSS recommendations on “open protocol” since IB is not generally in the public domain.	
345-346	47	**Comment:** The starting dose and estimated exposure levels chosen for all cohorts and study parts “as well as predefined adaption of these levels based on e.g. first PK results” should be pre-specified… Predefined criteria for adaptation of dose levels should be mentioned here: refer to section 7.3 line 401	Partly accepted. Text amended.
345-348	21	**Comments:** Integrated protocols can only be performed if they are adaptive and take into account emerging data for each decision. As mentioned above, in a combined FIH trial human pharmacokinetics are predicted, but not yet known. The starting dose is predefined, based on the appropriate calculations. All consecutive doses, including the maximum dose can be modelled and anticipated, but usually not predefined at the stage of trial design. Dosing regimen selection after the starting dose needs to take into account emerging PK, PD and safety/tolerability data to confirm or amend the anticipated dosing regimen selection. As long as a protocol contains clear pre-defined limits (such as starting dose, overall mean and individual PK exposure limits, maximum dose increments, exposure limits for consecutive study parts’ - e.g. MAD first dosing regimen -, potential pharmacodynamics limits) and dose escalation/progression rules, actual doses/dosing regimens should not be pre-defined. It is safer and more efficient to adapt doses/dosing regimens using emerging data within the limits of an adaptive protocol. Substantial amendments are only necessary if one wishes to go beyond the pre-defined limits. **Proposed change:** To amend the text as follows: “The starting dose, **overall mean and individual exposure limits, maximum dose increments, exposure limits for consecutive study parts’ (e.g. MAD first dosing regimen) and/or any pharmacodynamic limits** should be pre-specified, and justification for these **limits** should be outlined in the study protocol. Submission of a substantial amendment(s) can be used, if required, to adjust the pre-defined **limits**, depending	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		on data emerging during the CT.	
345-350	16	**Proposed change:** Would include here that PK sampling schemes might also need to be adjusted based on results of interim PK data, e.g. might need to add or could remove time points	Partly accepted. Text amended.
345-350	17	**Comments:** Modelling of animal data does not reliably predict actual exposure in humans. The guidance should not require applicants to pre-specify all dose levels and exposures planned in the first-in-human SAD trial, as the predicted exposures are unlikely to correspond to actual exposures. A rigid requirement to specify all dose levels is likely to result in unnecessary substantial amendments, which will delay study progress and potentially lead to withdrawal of subjects in crossover studies, thus compromising the scientific integrity of those studies and raising ethical issues about exposing additional volunteers to an experimental medicine. Instead, the protocol should specify the starting dose, maximum exposure and, where possible, the target exposure, based on the predicted therapeutic window. It should be acceptable to pre-specify dose selection rules as well as, or instead of, planned dose levels. Substantial amendments should be required for *significant* changes to pre-specified doses or to dose selection rules, or if (as stated in the draft guidance) the sponsor plans to increase exposure above the approved maximum. **Proposed change:** The starting dose ~~and estimated exposure levels chosen for all cohorts and study parts~~**, maximum exposure, and, if possible, target exposure (based on the therapeutic window) should be pre-specified and justified in the protocol**. T**he dose levels to be tested and/or the rules for dose escalation (eg maximum allowed fold increases in dose) should be pre-specified** and a justification for these steps should be outlined in the study protocol. Submission of a substantial amendment(s) can be used, if required, to **significantly** adjust the predefined **doses or** dosing selection **criteria**, depending on data emerging during the CT. Substantial amendments will also be needed where	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		dose escalation has reached a pre-defined maximum exposure and the absence of clinical effects leads to a conclusion that further careful escalation is warranted.	
345-350	18	**Comments:** We propose that more flexibility is provided with respect to a predefined dosing selection. We agree a starting dose and predefined maximum exposure are required and if the latter should need to be increased a substantial amendment would be required. Regarding prespecified estimated exposure levels, we propose this is replaced by dose escalation criteria and the reference to submission of a substantial amendment removed. **Proposed change:** From The starting dose and estimated exposure levels chosen for all cohorts and study parts should be pre-specified and a justification for these steps should be outlined in the study protocol. Submission of a substantial amendment(s) can be used, if required, to adjust the predefined dosing selection, depending on data emerging during the CT. Substantial amendments will also be needed where dose escalation has reached a pre-defined maximum exposure and the absence of clinical effects leads to a conclusion that further careful escalation is warranted. To The starting dose, dose escalation criteria and predetermined maximum exposure chosen for all cohorts and study parts should be pre-specified and a justification for these steps should be outlined in the study protocol. A substantial amendment will be needed where dose escalation has reached a pre-defined maximum exposure and the absence of clinical effects leads to a conclusion that further careful escalation is warranted.	Partly accepted. Text amended.
345-350	43	**Comments:** For oncology studies using adaptive (Bayesian) model-based design it is not necessary to pre-specify dose levels for all cohorts. Such approach allows exploring provisional dose levels as well as intermediate levels based on used emerging	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		data. The requirement of a substantial amendment in case of deviation from pre-defined dose levels or maximum dose is problematic and may not be applicable to oncology studies. This is described in a bit more balanced way in 7.3 (see 399-401). **Proposed change:** Add after L. 350 “In specific settings such as studies using adaptive model-based design, only provisional dose levels and exposures can be specified if the process for dose selection and the rules guiding this selection are clearly and prospectively described in the protocol.”	
346-399	47	**Comments:** Clarify “substantial amendment” versus an “amendment”.	Not accepted. Term ‘substantial amendment’ is widely used.
346-348	13	**Comments:** We propose to rephrase the following the following sentence “*Submission of a substantial amendment(s) can be used, if required, to adjust the predefined dosing selection, depending on data emerging during the CT*.” **Proposed change:** “***Substantial amendment(s) can be submitted,*** *if required, to adjust the predefined dosing selection, depending on data emerging during the CT*.”	Partly accepted. Text amended.
346-348	39	**Comments:** The wording should be more flexible and consistent with the line 399-402 (… Unless this possibility was discussed …)	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
346-348	47	Requirement for a 'substantial amendment' during FIH studies **Comments:** The guidance that "substantial amendment(s) can be used, if required, to adjust the predefined dosing selection" is not scientifically justified. PK, dose-response, and dose-toxicity relationships are often difficult to estimate from nonclinical studies, and certainly from in vitro studies. Therefore, dose escalation relationships cannot be precisely predicted. FIH is in the "learning" phase of drug development, the protocol doses are not selected to a priori satisfy a predefined dose-exposure-response relationship. Therefore, other than the starting and maximum dose justification, requiring justification of exposure for the in-between dose level are not useful. Some aspects in lines 346 and in 389 (intentionally or not) may restrict adaptive designs in the SAD part of a FIH. Protocols should be flexibly-written which define "maximum" dose escalation steps with flexibility to use prudence in smaller dose escalation steps, depending on emerging data. Such guidance is provided on Lines 421-423. Such flexibility will avoid unnecessary 'substantial amendment' generation and review. Suggest only require exposure for the starting, maximum and any critical dose level of therapeutic relevance, if known. Entry into human protocols should always specify a top exposure to be tested based on the totality of evidence approach. A substantial protocol amendment would then be needed to explore higher exposures than specified in the initial protocol. The guidance should permit flexibility in provisions for dose escalation so that a pre-specified departure from the planned nominal doses (within the range of starting dose and maximum permitted dose or exposure) is not a substantial amendment. As worded presently this is not consistent with provisions in section 8.25. Aligning text with section 8.2.5 will assure that intermediate or alternative dose levels can be easily substituted in response to emerging data in order to optimally characterize PK and PD (within pre specified dose selection criteria). Furthermore, in 400-402 allows for adjusting planned dose levels without a substantial amendment. **Proposed change:** "substantial amendment~~(s)~~ is not needed if the adjustments in predefined dose selection are clearly discussed in the	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		protocol and within the ~~can be used, if required, to adjust~~ predefined dose~~ing selection~~ escalation steps in response to emerging data". This proposed change then aligns with text in line #400-402.	
346-350	10	**Comments:** It is not clear whether a substantial amendment will be needed for any adjustment of the predefined dosing selection. A substantial amendment should only be necessary when the dose is increased above the predefined selection. The two sentences should be merged as follows. **Proposed change:** "Substantial amendments will also be needed <u>where the pre-defined dosing selection will be augmented (increase in predefined dose increments, higher than pre-defined maximum dose)</u> and also where dose escalation has reached a pre-defined maximum exposure and … is warranted."	Partly accepted. Text amended.
346-350	29	**Comments:** "The starting dose and estimated exposure levels chosen for all cohorts and study parts should be pre-specified and a justification for these steps should be outlined in the study protocol. Submission of a substantial amendment(s) can be used, if required, to adjust the predefined dosing selection, depending on data emerging during the CT. Substantial amendments will also be needed where dose escalation has reached a pre-defined maximum exposure and the absence of clinical effects leads to a conclusion that further careful escalation is warranted." It is common to adjust dose during dose escalation steps based on emerging pk and safety data from the study. If the procedure for deciding on dose selection is clearly stated in the protocol and the maximum step and top dose (or exposure) are not exceeded, it would be reasonable for this not to require a protocol amendment. **Proposed change:** <u>"The starting dose and estimated exposure levels chosen for all cohorts and study parts should be pre-specified and a justification for these steps should be outlined in the study protocol. If dose adjustments are intended during the CT then</u>	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		the rules for deciding on such dose adjustments should be clearly stated in the protocol. Such dose adjustments should not exceed the maximum justified dose increment nor the top dose stated in the protocol. Careful consideration should also be given to exposure to any significant metabolites in justifying the starting dose, dose increments and top dose. Submission of a substantial amendment(s) can be used, if required, to adjust the predefined dosing selection, depending on data emerging during the CT if such dose adjustments are not already clealy defined in the protocol. Substantial amendments will also be needed where dose escalation has reached a pre-defined maximum exposure and the absence of clinical effects leads to a conclusion that further careful escalation is warranted."	
346-350	33	**Comments:** It is not clear whether a substantial amendment will be needed for any adjustment of the predefined dosing selection or escalation process. A substantial amendment should only be necessary when the dose is increased above the predefined selection. See also discrepancy with the line 401.	Partly accepted. Text amended.
347	3	**Comments:** Clear circumstances which give rise to the need for substantial amendments to protocol are mentioned throughout the EMA Guidance. The first of these (line 347) states that "Submission of a substantial amendment(s) can be used, if required, to adjust the predefined dose selection." Pre-definition and justification remain a basic requirement.	General agreement.
347	26	**Comments:** ACRO is concerned by the term "predefined dosing selection" as not all doses can be determined definitively beforehand. However, if the protocol has predefined decision criteria, doses could be changed, within the margins of these criteria, without a substantial amendment. ACRO therefore recommends revision of the statement. **Proposed change:** Revise "to adjust the predefined dosing selection" to "to select dose levels outside the margins determined by predefined decision criteria."	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
347	40	**Comments:** In FTIH studies we would write the protocol with proposed doses, within the pre-specified dose range (based on previous data). But we allow flexibility within the protocol to alter the doses planned for the next cohort based on the emerging data without a protocol amendment. I am not sure this is allowed in line 347, where a substantial amendment is suggested. It suggests flexibility is allowed in lines 401-402, but this is not implied in this section.	Partly accepted. Text amended.
348-350	13	**Comments:** This sentence is an example of the previous sentence, therefore we propose to rephrase for clarity. **Proposed change:** "***For example****, substantial amendments will be needed where dose escalation has reached a pre-defined maximum exposure and the absence of clinical effects leads to a conclusion that further careful escalation is warranted.*	Partly accepted. Text amended.
348-350	14	**Comments:** This is a relatively common situation (reaching the highest planned dose level without identifying clinical effects). If the protocol includes the possibility of further dose escalation, it is not clear why a substantial amendment should be required to escalate beyond this dose level, since nothing is being amended. See also comment regarding line numbers 424-425. **Proposed change:** Suggest changing text to allow for inclusion of escalation beyond NOAEL if emerging data so permit, and as pre-specified in the protocol.	Partly accepted. Text amended.
348-350	30	**Comments:** It is not just the clinical effects that must be considered during dose escalation, but also the PK and especially the PD. Otherwise, as in the Bial trial, one might keep increasing the dose far past any maximal pharmacological effect until	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		toxicity occurs **Proposed change:** Substantial amendments will also be needed where dose escalation has reached a pre-defined maximum exposure and PK/PD analysis (and the absence of either adverse or therapeutic clinical effects) leads to a conclusion that further careful escalation is warranted.	
348-350	41	**Comments:** It is important that PK and PD data, and not just "clinical effects", are considered in relation to any dose escalation decision, including escalation above a pre-defined maximum. Escalation of the dose beyond the level at which there is unlikely to be any further increase in potential therapeutic benefit should not be considered, even in the absence of adverse clinical effects.	Partly accepted. Text amended.
351-353	17	**Comments:** Changes are required in line with the previous comment (lines 345–350). In addition, in line with the general comment on inclusion of information in both the IB and protocol, the guidance should allow sponsors flexibility in determining where it is appropriate to specify information on trial-specific calculations. **Proposed change:** The methods used and calculations on how doses**,** ~~and~~ **any** estimated exposure levels**, exposures in the therapeutic window, and maximum allowed exposure** were determined, including **any** methods for modelling (e.g. PK/PD and physiologically-based pharmacokinetic (PBPK)) should be included in the IB and**/or** ~~summarised in~~ the protocol.	Partly accepted. Text amended.
351-353	20	**Comments:** It seems inappropriate to include the detailed methods and calculations for dose predictions in the IB, especially if PBPK-based. This is likely to confuse, rather than inform, investigators. Also, this would generally become less relevant after	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		the clinical PK data are available, and therefore would only be important for the initial IB. A summary of approach and output in the IB and protocol seems sufficient. The methods and calculations could be provided in the CTA or in separate reports.	
351-353	47	**Comments:** It seems inappropriate to include the detailed methods and calculations for dose predictions in the IB, especially if PBPK-based. This is likely to confuse, rather than inform, investigators. Also, this would generally become less relevant after the clinical PK data are available, and therefore would only be important for the initial IB. Protocol should be enough to provide information on PK-PD modelling (not both IB and Protocol), as the modelling used may vary with the compound for a given study, and thus it would require the update of the IB for each and every study. **Proposed change:** A summary of approach and output in the protocol seems sufficient. The methods and calculations could be provided in the CTA or in separate reports.	Partly accepted. Text amended.
351-353	48	**Comments:** We would suggest that details of how doses are selected warrant inclusion in the study protocol. Information could therefore be summarized in the IB. **Proposed change:** The methods used and calculations on how doses and estimated exposure levels were determined, including methods for modelling (e.g. PK/PD and physiologically-based pharmacokinetic (PBPK)) should be ~~**included**~~ **summarized** in the IB and ~~**summarized**~~ **included** in the protocol.	Partly accepted. Text amended.
352	33	**Comments:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Modelling (PK/PD, PBPK) is not always available.	
354	13	**Comments:** The term Exploratory clinical trial requires further clarification. **Proposed change:** "*For starting and maximum doses for Exploratory Clinical Trials* ***(Phase 0 / early phase 1)*** *a reference is made to ICH M3(R2).*".	Not accepted. Term widely used.
354	20	**Comments:** The clarification with regards to studies done following a microdose study is useful, I would suggest however that stronger wording is used to reinforce this. **Proposed change:** If an IMP has been administered to humans under the paradigm of microdose trials, as outlined in ICH 355 M3(R2), any subsequent study using a non-microdose <u>will require the same detailed assessment for the starting dose</u>, and should be considered within the scope of this guideline	Not accepted. Too specific detail.
354	21	**Comments:** "Maximum doses" should be replaced by "maximum exposures". See above comments. **Proposed change:** To amend the text as follows: "For starting dose and **maximum exposures** for Exploratory Clinical Trials, reference is made to ICH M3(R2).	Partly accepted. Text amended.
350	40	**Comments:**	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Up until now in the document it is referring to FIH and early CT trials. This line now refers to 'Exploratory Clinical Trials'. Should it be clarified that this includes FIH and early CT trials, if ICH M3(R2) refers only to exploratory trials.	detail.
354	47	**Comments:** The clarification with regards to studies done following a microdose study is useful. Stronger wording should be used to reinforce this. **Proposed change:** "If an IMP has been administered to humans under the paradigm of microdose trials, as outlined in ICH 355 M3(R2), any subsequent study using a non-microdose will require the same detailed assessment for the starting dose, and should be considered within the scope of this guideline."	Not accepted. Too specific detail.
354-357	6	**Comments:** Although LEO Pharma, in general, is in agreement with the requirements as laid down in line 354-357, they seem to be extremely strict for exploratory studies with products that will be developed for topical treatment. **Proposed change:** Add a sentence after line 357: "Patch studies (psoriasis plaque studies, or comparable)", even if they do not completely fit in the definitions of ICH M3(R2), can normally be considered to be microdosing within the framework of this document, because of very low systemic exposure."	Not accepted. Too specific detail.
354-357	47	**Comments:** It should read for starting and maximal exposures rather than dose. **Proposed change:** "For starting and maximal doses exposures for exploratory…"	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
358	9	**Comments:** Please make reference to MABEL mandatory for all IMPs: small molecules and biologicals irrespective of high or low risk	Not accepted. As this is a guideline recommend-ations are not mandatory.
358	34	**Comments:** Consider including a dose conversion table that converts doses from animal (mouse, rat, rabbit, dog, monkey etc.) to human; similar to the US guidance document	Not accepted. Too specific detail.
358-387	26	**Comments:** ACRO recommends that Section 7.2. would benefit from the use of a flow chart or bullet points, emphasizing the step wise approach. **Proposed change:** Include a flow chart or bullet points to emphasize the step wise approach.	Not accepted. Too specific detail.
358-387	47	**Comments:** A distinction should be made around the potential differences in starting dose for FIH and in early CTs, and this should be described in the guidance.	Not accepted. Too specific detail.
358-387	47	**Comments:** This section implies that safety margins should be applied to all calculations (NOAEL, MABEL, PAD, ATD) and does not give consideration to the use of different safety margins for different methods. Given the vastly different dose projections that usually come from these different methods, this could lead to errors in dosing.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: line 382 – "Any safety factors used, recognizing that different factors may be used for the different metrics, should be documented and detailed in the IB and protocol".	
359	26	**Comments:** ACRO recommends including a more precise definition of NOAEL, because NOAEL is sometimes interpreted differently, e.g. NOAEL could be the highest dose level that did not produce a toxic effect in preclinical studies or the highest dose that does not produce a toxic effect which would be unacceptable in the first dose in humans. **Proposed change:** Include a more precise definition of NOAEL.	Partly accepted. Text amended.
359	47	**Comment:** The Starting dose based on NOAEL is applicable to healthy volunteer. For example, starting dose for patients (e.g. oncology) are based on STD10 or 1/6 of HNSTD in the most sensitive species. **Proposed change:** In general, for FIH studies conducted in healthy volunteers, the no observed adverse effect level (NOAEL) should be determined in the non-clinical safety studies performed.	Partly accepted. Text amended – section now refers to healthy volunteers.
359-360	14	**Comments:** "In general, the no observed adverse effect level (NOAEL) should be determined in the non-clinical safety studies performed." This is redundant in the context of a guideline concerned with mitigating clinical risk in FIH trials.	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Suggest reverting to language in the current guideline ("In general, the No Observed Adverse Effect Level (NOAEL) determined in non-clinical safety studies performed in the most sensitive and relevant animal species, adjusted with allometric factors […] or on the basis of pharmacokinetics gives the most important information. The relevant dose is then reduced/adjusted by appropriate safety factors according to the particular aspects of the molecule and the design of the clinical trials.")	
359-361	43	**Proposed change:** Move the information on starting dose in patients (section 7.7, L. 454-461) to this section.	Partly accepted. Text amended.
359-363	26	**Comments:** To ensure clarity of decision making for the starting dose, ACRO recommends that the guideline should state that the derivation of the NOAEL and the estimation of equivalent exposure for humans are reported and explained in the Investigator Brochure. **Proposed change:** Add the following statement: "The derivation of the NOAEL and the estimation of equivalent exposure for humans should be reported and explained in the Investigator Brochure."	Partly accepted. Text amended.
359-363	30	**Comments:** This paragraph is out of position and should follow the subsequent paragraph (starting Exposure showing …) The default for selection of starting dose should be the Pharmacologically Active Dose / MABEL for small as well as large molecules. The NOAEL provides guidance to the maximum recommended starting dose but the PAD/MABEL will generally provide a much more relevant starting dose, which will be much lower. Lines 374-5 are relevant only to the NOAEL. Generally, a safety factor is not required for doses based on the PAD.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
359-363	47	**Comments:** The topic of estimation of exposure in humans using exposures in most relevant and sensitive animal species based on state-of-the-art modelling (e.g. PK/PD and PBPK) and/or using allometric factors is quite relevant. However, the modelling part may not always be feasible due to various reasons such as no known relevant PD marker, lack of PK/PD correlation in animal species (especially at the high doses). While it is agreed that there should understandably be always an attempt to take the most informed decision in deciding doses for the first in man studies, it would be helpful to word the last statement in the paragraph above a bit differently. **Proposed change:** Whenever feasible, estimation should be based on allometric factors or state-of-the-art modelling (e.g. PK/PD and PBPK).	Partly accepted. Text amended.
359-363	47	**Comments:** "In general, the no observed adverse effect level (NOAEL) should be determined in the non-clinical safety studies performed. The exposures achieved at the NOAEL in the most relevant and sensitive animal species used should then be used for estimation of an equivalent exposure for humans. Estimation should be based on state-of-the-art modelling (e.g. PK/PD and PBPK) and/or using allometric factors." **Proposed change:** Suggest rephrasing to: "In general, the no observed adverse effect level (NOAEL) should be determined in the non-clinical safety toxicology studies performed. In non-clinical safety pharmacology studies a NOAEL setting is not required. However, effects should be taken into consideration when setting the starting dose. The exposures achieved at the NOAEL in toxicology studies and at effect levels observed in safety pharmacology studies in the most relevant and sensitive animal species used, should then be used for estimation of an equivalent exposure for humans. Estimation should be based on state-of-the-art modelling (e.g. PK/PD and PB/PK) and/or using allometric factors."	Partly accepted. Text amended.
359-	22	**Comments:**	Accepted. Text

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
387		Section 7.2 on starting dose is quite confusing:. It is not clear from text why a MABEL estimate would be needed on a routine basis. This was explained in the current guideline. This section lack a clear step-by-step description of what data agencies need to see, and why. **Proposed change:** This is a critical section for the whole guideline, and needs to be re-written in a format that is comprehensible also to new entrants (academics; start-up companies).	amended.
360-361	20	**Comments:** The most relevant species is not always the most sensitive species. We suggest deleting “and sensitive” from this sentence, and adding a statement that when the most relevant species is not the most sensitive species, the rationale for not using the most sensitive species should be provided. It may also be helpful to refer to the FDA Guidance around definition of “the most relevant and sensitive animal species.”	Partly accepted. Text amended.
360-361	34	**Comments:** The most relevant species is not always the most sensitive species. **Proposed change:** Consider deleting “and sensitive” from this sentence, and adding a statement that when the most relevant species is not the most sensitive species, the rationale for not using the most sensitive species should be provided	Partly accepted. Text amended.
361	47	**Comments:** inaccurate language, because the human equivalent dose (HED) is based on similar exposure **Proposed change:**	Not accepted. The focus is on exposure.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Amend text to "…estimation of an equivalent dose ~~exposure~~ for humans."	
362	33	**Comments:** Modelling is not always available. **Proposed change:** modelling (e.g. PK/PD and PBPK) when available and/or using allometric factors.	Partly accepted. Text amended.
362-363	16	**Proposed change:** Provide modeling and allometric examples or include references?	Not accepted. Too specific detail.
362-363	47	**Comments:** Suggestion to replace "estimation" by scaling the NOAEL to humans as scaling implies taking differences between species such as physiology, expression levels of enzymes/transporters, protein binding etc. into account **Proposed change:** Scaling between species should be based on allometry and/or modelling approaches taking differences between species into account.	Not accepted. Too specific detail.
364	46	**Comments:** I think the first sentence should say "Safe exposure associated with PD effects...."	Not accepted. Too specific detail.
364-367	13	**Comments:** Split into two sentences to improve readability: "*Exposure showing PD effects in the non-clinical pharmacology studies, including ex vivo and in vitro studies in human tissues if feasible, should also be determined and these data should be*	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		*used to **determine. These data** should be used to determine the minimal anticipated biological effect level (MABEL) in humans and an estimation of the pharmacologically active dose (PAD) and/or anticipated therapeutic dose range (ATD) in humans."*	
364-367	21	**Comments:** In line with the above, we suggest adding the terms "pharmacologically active exposure" and "anticipated therapeutic exposure range". In clinical pharmacology practice, it is often the emerging exposure data during a trial that determines selection of consecutive doses. **Proposed change:** To amend the text as follows: […] and an estimation of the **pharmacologically active exposure and/or** pharmacologically active dose and/or **anticipated therapeutic exposure range and/or** anticipated therapeutic dose range.	Not accepted. Too specific detail.
364-367	47	**Comments:** For small molecules, the presence of major metabolites and their relevance for activity or toxicity should also be considered when selecting starting dose. **Proposed change:** "Exposure showing PD effects in the non-clinical pharmacology studies, including ex vivo and in vitro studies in human tissues if feasible, should also be determined and these data should be used to determine the minimal anticipated biological effect level (MABEL) in humans and/or an estimation of the pharmacologically active dose (PAD) and/or anticipated therapeutic dose range (ATD) in humans. Presence of major active metabolite needs to be taken into consideration."	Not accepted. Too specific detail.
364-	51	**Comments:**	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
367		Anticipated therapeutic dose range (ATD) appears to be a new term that is not in common use. BIO asks EMA to define and discuss the term in more detail. This also introduces a new element, not just estimating the starting dose but also providing a full exposure-response relationship estimate for humans. Finally, the use of "therapeutic" in this sense seems to imply some prior knowledge of the level of target engagement/PD that is required for clinical efficacy.	detail.
364-369	47	**Comments:** It would be useful to clearly shown how MABEL, PAC and ATD differ. For example, what does minimal mean? Should A be redefined as "acceptable"? Some guidance on "Biological Effect" would be helpful. Together this would ensure that the MABEL dose addresses safety and not just any biological effect.	Not accepted. Too specific detail.
364-369	51	**Comments:** BIO believes it would be useful to clearly show how MABEL, PAC and ATD differ. For example, what does minimal mean? BIO suggests re-defining this term by replacing "anticipated" with "acceptable". Using "acceptable" would link this term to the risk-assessment. Additionally, some guidance on "Biological Effect" would also be helpful (*i.e.,* any biological effect or a biological effect that may result in an AE). Together this would ensure that the MABEL dose addresses safety and not just any biological effect. **Proposed change (of any):** Exposure showing PD effects in the non-clinical pharmacology studies, including ex vivo and in vitro studies in human tissues if feasible, should also be determined and these data should be used to determine the minimal <u>acceptable</u> ~~anticipated~~ biological effect level (MABEL) in humans and an estimation of the pharmacologically active dose (PAD) and/or anticipated therapeutic dose range (ATD) in humans.	Not accepted. Too specific detail.
364-373	23	**Comments:** The concept of anticipated therapeutic dose range (ATD) is not clear in view of safety and tolerability testing in early clinical development, especially since the draft guidance further details in lines 424 and 425 that in general the ATD	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		should not be exceeded in studies in healthy volunteers, unless scientifically justified. This implies that in case the initial ATD is estimated too conservative, the ATD might need to be adjusted during development, based on an increasing understanding of pharmacology and efficacy data. As such there is a risk for additional or repeat studies to investigate safety and tolerability at higher exposures in later development. Though the current wording in the draft guidance still provides flexibility based on scientific justification, it is considered important as a general approach to explore the full safety range in early development under strictly controlled Phase I conditions to allow later dose adjustment or supra-therapeutic investigations (e.g. QTc).	
364-373	37	**Comments:** We agree that all available *in vitro* and *in vivo* data should be taken into account to determine not only MABEL, but PAD and ATD. We also suggest that any additional non-clinical information that can help guide PK-PD modelling (e.g. interaction with transporters, Cytochrome P450 enzymes, Biopharmaceutics Drug Disposition Classification etc) should be considered where possible.	Not accepted. Too specific detail.
364-375	26	**Comments:** To ensure clarity of decision making for the starting dose, ACRO recommends that the guideline should state that the calculations of MABEL, PAD and/or ATD are reported and explained in the Investigator Brochure. **Proposed change:** Add the following statement: “The calculations of MABEL, PAD and/or ATD should be reported and explained in the Investigator Brochure.”	Partly accepted. Text amended.
366	10	**Comments:** In the previous guideline, the MABEL approach was only requested for IMPs for which factors influencing risks according to section 4.1 have been identified (e.g. biologics). In the current revision, this differentiation is not mentioned with	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		respect to the determination of MABEL. **Proposed change:** A specification for the applicability of MABEL should be added in section 7.2.	
366	33	**Comments:** In the previous guideline, the MABEL approach was only requested for IMPs for which factors influencing risks according to section 4.1 have been identified (e.g. biologics). In the current revision, this differentiation is not mentioned with respect to the determination of MABEL. **Proposed change:** A specification for the applicability of MABEL should be added in section 7.2.	Not accepted. Too specific detail.
366	47	**Comments:** Given the confusion surrounding the terminology for MABEL, perhaps this is an opportunity to try to re-define this term by replacing “anticipated” with “acceptable”. Using “acceptable” would link this term to the risk-assessment. **Proposed change:** Exposure showing PD effects in the non-clinical pharmacology studies, including ex vivo and in vitro studies in human tissues if feasible, should also be determined and these data should be used to determine the minimal acceptable anticipated biological effect level (MABEL) in humans and an estimation of the pharmacologically active dose (PAD) and/or anticipated therapeutic dose range (ATD) in humans.	Not accepted. Too specific detail.
366	47	**Comments:** In the previous guideline, the MABEL approach was only requested for IMPs for which factors influencing risks according to section 4.1 have been identified (e.g. biologics). In the current revision, this differentiation is not mentioned with	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		respect to the determination of MABEL. **Proposed change:** Add specification for the applicability of MABEL in section 7.2.	
367	22	**Comments:** It is suggested to define ATD more precisely	Not accepted. Too specific detail and term is commonly used.
367	26	**Comments:** ACRO is concerned by the use of “and/or” in this sentence as we consider that the estimation of the anticipated therapeutic dose (ATD) range should not be optional. If possible, the ATD should be compared with the anticipated dose/exposures at which significant toxicities occur in animals since this comparison may reveal that the compound has an insufficient safety margin and further development should not continue. **Proposed change:** Change “and/or” to “and”.	Not accepted. Too specific detail.
367	47	**Comments:** Anticipated therapeutic dose range (ATD) appears to be a new term. As such, it should be defined and discussed in more detail. This also introduces a new element, not just estimating the starting dose but also providing a full exposure-response relationship estimate for humans. And, the use of “therapeutic” in this sense seems to imply some prior knowledge of the level of target engagement/PD that is required for clinical efficacy. **Proposed change:**	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Agency to define Anticipated Therapeutic Dose range.	
369-372	13	**Comments:** The paragraph mentions 3 times determination/calculation of MABEL, PAD and/ or ATD. We suggest to reword the following sentences to improve readability: "*In addition, the calculation of the MABEL, PAD and/or ATD should consider target binding and receptor occupancy studies in vitro in target cells from human and the relevant animal species and exposures at pharmacological doses in the relevant animal species.*" → "***In addition, target binding and receptor occupancy studies in human target cells, in vitro, and relevant animal species, in vivo, should be considered. In the relevant animal species exposure at pharmacological doses should be considered as well.***	Partly accepted. Text amended.
369-373	51	**Comments:** The description in the paragraph is referring to the calculation of the starting dose. The three methods mentioned: MABEL, PAD and ATD do not necessarily incorporate target binding or receptor occupancy. It is rather a PKPD approach that can take into account multiple parameters. Therefore, this sentence could be clarified to state that the predicted target occupancy or amount of target binding should be calculated at the dose levels proposed as starting doses. **Proposed change:** In addition, the <u>starting dose propositions based on</u> MABEL, PAD and/or ATD should consider <u>the predicted</u> target binding and target occupancy studies in vitro in target cells from human and the relevant animal species and exposures at pharmacological doses in the relevant animal species. Whenever possible, all relevant data should be integrated in a suitable modelling approach for the determination of the MABEL, PAD and/or ATD.	Not accepted. Too specific detail.
371	20	**Comments:** Plasma protein binding differences should also be considered **Proposed change:**	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		….and the relevant animal species and free exposures at pharmacological doses….	
371	47	**Comments:** In the previous guideline, the MABEL approach was only requested for IMPs for which factors influencing risks according to section 4.1 have been identified (e.g. biologics). In the current revision, this differentiation is not mentioned with respect to the determination of MABEL. **Proposed change:** Add specification for the applicability of MABEL in section 7.2.	Not accepted. Too specific detail.
372	5	**Comments:** Wording such as 'whenever possible' should be avoided. **Proposed change:** Please specify the best practice and what should be done when best practice is not possible.	Not accepted. Too specific detail. Not accepted. Too specific detail.
372	46	**Comments:** For CNS indications, there should be a need to estimate blood brain barrier penetration.	Not accepted. Too specific detail.
372	47	**Comments:** Please clarify what a “suitable modelling approach” is in this case.	Not accepted. Too specific detail.
372-375	10	**Comments:** The guideline does not consider pathogen-specific molecules, for which e.g. a MABEL cannot be calculated.	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please adjust the guideline accordingly.	
373	47	**Comments:** This guideline currently considers primarily human cellular molecules as pharmacological target, but not pathogen specific molecules, for which e.g. MABEL cannot be calculated. Therefore, we would propose to add information on this by adding one sentence here. **Proposed change:** Add the following sentence between original lines 373 and 374: **Under certain circumstances, e.g. for anti-infectives, MABEL and PAD is not applicable in healthy volunteers and exposure-response is studied instead in in-vivo infection models for calculation of e.g. ED50 and ED100.** line 383: **When the methods of calculation (e.g. NOAEL and MABEL, if applicable) give different estimations of the starting dose for humans, the lowest value should be used, unless justified.**	Not accepted. Too specific detail.
374-375	20	**Comments:** " *In order to further limit the potential for adverse reactions in humans, a safety factor(s) is generally applied in the calculation of the starting dose in humans.*" Please define the safety factor.	Not accepted. Too specific detail.
374-375	26	**Comments:** ACRO recommends adding clarification as to whether the safety factor should be applied to both the NOAEL and MABEL	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		calculations. **Proposed change:** Clarify whether the safety factor should be applied to both the NOAEL and MABEL calculations.	
374-375	47	**Comments:** If a safety factor is always used when the MABEL is used for setting the starting dose this may result in an unnecessary low starting dose. **Proposed change:** Suggest making statement less strict e.g. like in current version of guideline "A safety factor may be applied for the calculation of first dose in human from MABEL." Or alternatively to include rationality, as e.g.: “A safety factor is generally applied in the calculation of the starting dose in humans, unless justification is provided that no safety factor is needed.”	Not accepted. Too specific detail.
376	20	**Comments:** There is no mention of NOAEL doses or exposures for assessing Safety factors/margins. Suggest adding: “safety factors should take into account potential risks related to NOAEL doses and exposures, novelty of the active substance ……..”	Not accepted. Too specific detail.
376	34	**Comments:** There is no mention of NOAEL doses or exposures for assessing Safety factors/margins. **Proposed change:** Consider ”Safety factors should take into account potential risks related to NOAEL doses and exposures, novelty of the active substance, …”	Not accepted. Too specific detail.
377-	13	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
378		The use of brackets in this sentence, because the part is an example and not a part of the enumeration. "*Safety factors should take into account potential risks related to the novelty of the active substance, its pharmacodynamic characteristics* ***(including irreversible or long lasting findings and the shape of the dose-response curve)****, the relevance of the animal models used for safety testing, uncertainties related to the estimation of the MABEL, and the expected exposure in humans."*	Text amended.
379	46	**Comments:** should read "the expected exposure and monitorability in humans"	Not accepted. Too specific detail. Covered in the next sentence.
382	16	**Comments:** No specific recommendations for how to calculate the starting dose are provided. I was expecting to see another guidance referenced that is specific to determining the starting dose (as the FDA has), but I don't see it.	Not accepted. Too specific detail.
382	17	**Comments:** Safety factors here apply only to the starting dose in a first-in-human SAD study: they are trial-specific, and are best placed in the protocol. **Proposed change:** Any safety factors used should be justified and detailed in the protocol.	Partly accepted. Text amended.
382	30	**Comments:** It is unnecessary to duplicate information in both IB and protocol. The IB is not specific to any single CT. At the FIH stage, there are no other CTs. The risk-benefit section of the IB will need updating before any other trial can start, other sections don't. The IB should contain all the information available; this information and justifications for decisions made	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		should be summarised in the protocol. **Proposed change:** Any safety factors used should be justified and detailed in the protocol.	
382	47	**Comments:** Safety factor - The EMA guideline states that the safety factor needs to be justified. However, given the empirical nature of the safety factor, it is unclear how it can be justified. Importantly, both the Tegenero and our internal experience indicate that the empirical safety factor offers no protection for human safety. Safety factor is very subjective, a better understanding of the compound itself and its preclinical data is more justified than a safety factor.	Partly accepted. Text amended.
382	47	**Comments:** "….justified and detailed in the IB and protocol." Details regarding projected efficacious dose calculations in the IB are proposed as a requirement for 1st IB (preFIH) but not needed when IB is updated post initiation of clinical trials. **Proposed change:** Clarification to text requested - "….justified and detailed in the initial IB and in the protocol."	Partly accepted. Text amended.
382-385	3	**Comments:** Welcome also, in the RSS spirit of "open protocol", is the requirement (line 382) that: "Any safety factors used should be justified and detailed in the IB and protocol". Likewise (lines 383-385) when methods of calculation give different estimations of the starting dose for humans.	Partly accepted. Text amended.
382-385	21	**Comments:** For FIH trials, it is often the CT protocol that describes starting dose calculations and safety factors, rather than the IB. Duplication should be avoided.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: To amend the text as follows: “Any safety factors should be justified in the IB and**/or** protocol.” […] “Such a justification should be included in the IB and**/or** CT protocol.”	
382-385	47	**Comments:** If the doses are explained in the protocol and are related to non-clinical data why is this extra "safety factor justification" needed? It is already in line 376 stated that a safety factor should be applied. **Proposed change:** Suggest delete the line. Add "safety pharmacology effect level" in front of "and MABEL) give different estimations of the starting dose for humans, the lowest value should be used, unless justified. Such a justification should be included in the IB and CT protocol."	Partly accepted. Text amended.
382-387	47	**Comments:** The estimation of the starting dose for humans (i.e. method of calculation, i.e. using NOAEL or MABEL, as well as related safety factors) should take into account the factors as outlined in section 4, specifically factors regarding the novelty and nature of the MoA including the extent of available data on previous exposure of humans to compounds with similar MoA	Partly accepted. Text amended.
383	34	**Comments:** When discussing the use of NOAEL versus MABEL, the revised guidance notes the lowest value should be used, “unless justified.” “Unless justified” is vague and may lead to inappropriate use of MABEL in situations where the use of NOAEL is more appropriate. The original guidance was clear in specifying the use of MABEL rather than NOAEL and similar wording should be considered: “For investigational medicinal products for which factors influencing risk…have been identified; an additional approach to dose calculation should be taken. Information about pharmacodynamics can give further guidance for dose selection. The ‘Minimal Anticipated Biological Effect Level’ (MABEL) approach is recommended.”	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Consider "When the methods of calculation of safety margins (eg NOAEL and vs MABEL) give different……."	
383-384	47	**Comments:** Starting dose language should be softened. Proposed change: "***In absence of justification***, when the methods of calculation (e.g. NOAEL and MABEL) give different estimations of the starting dose for humans, the lowest value should be used, unless justified." What would the definition of biological effect be for a small molecule in relation to MABEL. **Proposed change:** The biological effect dose/exposure considerations should be primarily derived from in vivo studies with measurement of a meaningful change in endpoint.	Partly accepted. Text amended.
383-385	10	**Comments:** In the way it is described now, MABEL would determine the starting dose of many NMEs. This is too conservative and does not allow a differentiation between NMEs with different risk potential. The use of MABEL should be reserved for those compounds for which the mode of action/nature of target/relevance of animal species revealed an increased risk. **Proposed change:** Remove the bracket term in line 383	Partly accepted. Text amended.
383-385	33	**Comments:** The use of MABEL should be reserved for those compounds for which the mode of action/nature of target/relevance of animal species revealed an increased risk.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Remove the bracket term in line 383	
383-385	47	**Comments:** The guideline is advocating to use the lower of the NOAEL and the MABEL (hence for biologics this will almost always be the MABEL) as a starting dose, unless providing justification for not using it. It is stated (line 386) that the starting dose should have no PD response (at least in HVs). This is overly conservative for highly specific biologics (especially for antagonists against soluble targets) and depends on the pharmacological pathway that is being targeted and if the molecule is considered a high risk molecule (i.e. all the considerations assessed in sections 4.1-4.4). The concept of duration of PD response should be included i.e that it may be acceptable (dependent on risk) to have a PD response at the starting dose but only for a short duration, dependent on the perceived risk. Molecules are risk-classified (high vs low) based on the considerations laid out in section 4.1-4.4). For lower risk biologics, a MABEL approach may not be needed (this would be the 'justification' but what these examples of justifications might be should be clarified in the guidance- again referencing back to the text in section 4.1-4.4). Otherwise readers might think that we should use MABEL for all mAbs and only in certain situations would we not (for the majority of mAbs inhibiting soluble mediators, especially those against mediators with a clinical history of safe modulation, then the MABEL would be overly conservative). The statement in line 383 “When the methods of calculation (e.g. NOAEL and MABEL) give different estimations of the starting dose for humans, the lowest value should be used, unless justified.” is not aligned with ICH M3(R2) guidance which states that “In general, the No Observed Adverse Effect Level (NOAEL) determined in nonclinical safety studies performed in the most appropriate animal species gives the most important information.” and should be discussed in the ICH environment. **Proposed change:** “~~When the methods of calculation (e.g. NOAEL and MABEL) give different estimations of the starting dose for humans, the lowest value should be used, unless justified.~~ Justification for not using the MABEL may include the molecule being	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		considered having a low safety risk based on the pharmacological risk considerations described in section 4.1 to 4.4. Such a justification should be included in the IB and CT protocol"	
383-385	51	**Comments:** The guideline is advocating to use the lower of the NOAEL and the MABEL (hence for biologics this will almost always be the MABEL) as a starting dose, unless providing justification for not using it. It is stated (line 386) that the starting dose should have no PD response (at least in healthy volunteers). This is overly conservative for highly specific biologics (especially for antagonists against soluble targets) and depends on the pharmacological pathway that is being targeted and if the molecule is considered a high risk molecule (*i.e.,* all the considerations assessed in sections 4.1-4.4). The concept of duration of PD response should be included *i.e.,* that it may be acceptable (dependent on risk) to have a PD response at the starting dose but only for a short duration, dependent on perceived risk. Molecules are risk-classified (high vs low) based on the considerations laid out in section 4.1-4.4). For lower risk biologics a MABEL approach may not be needed (this would be the 'justification' but what these examples of justifications might be should be clarified in the guidance-again referencing back to the text in section 4.1-4.4). Otherwise it is possible that readers will think that the MABEL should be used for all mAbs. **Proposed change:** For molecules associated with a certain level of risk triggering the use of the MABEL, when the methods of calculation based of NOAEL or MABEL give different estimations of the starting dose for humans, the lowest value should be used; ~~justified. Justification for not using the MABEL may entail the molecule being considered having a low safety risk based on the pharmacological risk considerations described in section 4.1 to 4.4.~~ Justification should be included in the IB and CT protocol.	Partly accepted. Text amended.
383-387	12	"*When the methods of calculation (e.g. NOAEL and MABEL) give different estimations of the starting dose for humans, the lowest value should be used, unless justified. Such a justification should be included in the IB and CT protocol. In healthy volunteers, the starting dose should ideally result in an exposure to a subject that is below that which would be expected*	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		to produce a PD response." (Section "7.2. Starting dose") **Comments:** The statement "*When the methods of calculation (e.g. NOAEL and MABEL) give different estimations of the starting dose for humans, the lowest value should be used, unless justified*" is **not in the spirit of ICH M3(R2) guidance** which states that "*In general, the No Observed Adverse Effect Level (NOAEL) determined in nonclinical safety studies performed in the most appropriate animal species gives the most important information.*" In addition, according to ICH M3 (R2) guidance, the starting dose calculation in the exploratory clinical trials is based on NOAEL. There should be discrimination in the estimation of the starting dose between compounds considered as high-risk compounds (based on mode of action, target, pharmacodynamics) and other compounds for which a NOAEL-based estimation of the starting dose can be applied. **Proposed change:** Overall, this statement which is not in the spirit of ICH guidelines should be discussed in the ICH expert group before unilateral implementation in Europe.	
385	30	**Comments:** As above [It is unnecessary to duplicate information in both IB and protocol. The IB is not specific to any single CT. At the FIH stage, there are no other CTs. The risk-benefit section of the IB will need updating before any other trial can start, other sections don't. The IB should contain all the information available; this information and justifications for decisions made should be summarised in the protocol.] **Proposed change:** Such a justification should be included in the protocol.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
386	30	**Comments:** Meaning of the word 'subject' is unclear. Presumably it means 'participant'. However, this is not needed. The sentence is clear without it. To reinforce the word ideally, an explanation should be requested if this is not planned in the protocol As noted in Section 7.1 (lines 336-338), dose selection should also take into account a reasonably rapid attainment of the trial objectives (…) without exposing large numbers of subjects. The selected should therefore not be far below the expected pharmacological dose. **Proposed change:** In healthy volunteers, the starting dose should ideally result in an exposure that is below, but expected to be close to, that which would be expected to produce a PD response. If this is not possible, an explanation should be given in the protocol.	Partly accepted. Text amended.
386	47	**Comments:** Having such a starting dose should be relevant for patients too; otherwise a special phrase for what to do in case the FIH study is conducted in patients should be included. Of course, in oncology patients or other patients with serious diseases, e.g., such an approach would be unethical. **Proposed change:** Suggest delete "In healthy volunteers" and start sentence with "The starting dose…."	Partly accepted. Text amended.
386-387	13	**Minor text comment:** "*In healthy volunteers, the starting dose should ideally result in an exposure* ***that is below the exposure which is expected*** *to produce a PD response*."	Partly accepted. Text amended.
386-	14	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
387		"…the starting dose should **ideally** result in an exposure…" "Ideally" is somewhat weak; stronger language should be employed. **Proposed change:** "In healthy volunteers, the starting dose should ~~ideally~~ result in an exposure to a subject that is below 386 that which would be expected to produce a PD response**, unless specifically justified in the protocol.**"	Text amended.
386-387	20	**Comments:** This statement "likely to produce a PD response" is very ambiguous and could lead to either under- or over-dosing depending on interpretation. For instance, is this an expected intra-cellular response that can never be measured and occurs at very low exposures, or a measurable physiological outcome that is routinely measured, or a response that is measurable depending on assay sensitivity? **Proposed change:** "In healthy volunteers, the starting dose should ideally result in an exposure to a subject that is a fraction of the projected efficacious plasma concentration expected to produce a PD response."	Partly accepted. Text amended.
386-387	22	**Comments:** It should be made clear in relation to lines 374-375 that the safety factor applied will result in an exposure below the one exerting PD effects. **Proposed change:** Please consider combining lines 386-387 with 374-375 in one paragraph	Partly accepted. Text amended.
386-387	47	**Comments:** The starting dose in HV should not necessarily result in an exposure that is below that which would be expected to	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		produce a PD response. Classes of drugs, which already have a reasonably well established dose-responses and/or tox responses should not need to follow this path. For instance, is this an expected intra-cellular response that can never be measured and occurs at very low exposures, or a measurable physiological outcome that is routinely measured, or a response that is measurable depending on assay sensitivity? **Proposed change:** "In healthy volunteers, the starting dose should ideally result in an exposure to a subject that is below that which would be expected to produce an unacceptable PD response and below the anticipated therapeutic exposure range."	
386-387	48	**Comments:** The language related to the use of a starting dose that does not elicit any PD effect when conducting studies in healthy subjects would seem to render such an approach meaningless. While we accept the need for caution, we would suggest a minimal PD effect could be justified in order to generate meaningful data from the exposure of a healthy subject to a test agent. **Proposed change:** In healthy volunteers, the starting dose should ideally result in an exposure to a subject ~~**that is below that**~~ which would be expected to produce a **minimal** PD response **or has minimal biological activity**.	Partly accepted. Text amended.
386-387	51	**Comments:** The starting dose in healthy volunteers should not necessarily result in an exposure that is below that which we would expect to produce a PD response. Classes of drugs which already have a reasonably well established dose-response and/or toxicology response do not need to follow this path. **Proposed change:** In healthy volunteers, for novel molecules against novel targets, the starting dose should ideally result in an exposure to	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		a subject that is below that which would be expected to produce a PD response. However for well-defined classes of drugs against targets/pathways for which there is already a reasonably well established dose/exposure/PD/toxicology, a PD response of limited magnitude and duration could be acceptable.	
388	30	**Comments:** It should be made clear from the first sentence of this section that dose escalation must be made on the basis of a comprehensive review of accumulating tolerability, safety, PK and, when relevant, PD data from previous doses.	Partly accepted. Text amended.
388-404	23	**Comments:** In case a FIH trial is conducted in patients, even with a primary safety/tolerability objective, criteria for dose selection and dose escalation should also include the ethical consideration of not exposing too many patients to sub-therapeutic doses (e.g. in oncology drug development). This factor is not currently accounted for in section 7.3 (Dose escalation) and for overall clarity it is suggested to add the sentence proposed below. **Proposed change:** **"In case a FIH trial is conducted in patients, even with a primary safety/tolerability objective, criteria for dose selection and dose escalation should also include the ethical consideration of not exposing too many patients to sub-therapeutic doses (e.g. in oncology drug development)."**	Partly accepted. Text amended.
388-404	47	**Comments:** A distinction should be made around the potential differences in dose escalation for FIH and early CTs, and this should be described in the guidance.	Not accepted. Too specific detail.
388-404	47	**Comments:** PK, dose-response, and dose-toxicity relationships are often difficult to estimate from nonclinical studies, and certainly from *in vitro* studies. Therefore, dose escalation relationships cannot be precisely predicted. Consideration should be	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		given for flexibly-written protocols which define "maximum" dose escalation steps with flexibility to use prudence in smaller dose escalation steps, depending on emerging data. Such guidance is provided on Lines 421-423. Such flexibility will avoid time-consuming substantial amendment generation and review.	
389	47	**Proposed change:** Pre-define rate of dose increase and a maximum exposure based on pre-clinical work. Within those limits should be able to make decisions based on current observations. Another option may be a partnering authority or ethics committee who is part of the review process without delaying timelines.	Partly accepted. Text amended.
389-391	16	**Proposed change:** Would provide more details on AEs of interest that should be reviewed (at a minimum), for example: QT interval, LFTs, etc..	Not accepted. Too specific detail.
389-402	49	**Comments:** In the BIAL/Biotrial clinical trial, the desired effect of the drug in humans was observed at much lower doses than anticipated. The EMA Guidelines should give a clear recommendation to reconsider the planned dose-escalation in such cases.	Partly accepted. Text amended.
390-391	13	**Comments:** Reorder the wording of the following sentence to improve readability: "*The choice of the subsequent dose levels should include some estimate of the potential PD effects and exposure levels to be achieved as well as adverse effects seen (if any).*" → "*The choice of the subsequent dose levels should include* ***an estimate of the exposure levels to be achieved and the potential PD effects and adverse effects seen (if any).***"	Partly accepted. Text amended.
390-	17	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
391		It might not always be possible or necessary to measure PD directly, eg in studies of new antibiotics, or where the target is under-expressed in healthy volunteers compared with patients with the target disease. Also, where several measures of PD are made, it should be possible to pre-specify in the protocol, with justification, which variables will be reviewed during dose selection. **Proposed change:** subsequent dose levels should include some estimate of the ~~potential PD effects and~~ exposure levels to be achieved as well as adverse effects seen (if any) **and, when feasible, an estimate of the potential PD effects**.	Text amended.
390-391	20	**Comments:** Similar to comment for lines 345, the requirement to justify PK and PD estimates for the in-between doses are not useful Suggest focus on starting and maximum and therapeutic dose levels	Partly accepted. Text amended.
390-391	47	**Comments:** An estimate of the PD effects at various dose levels would depend on the availability of a suitable and translatable PD marker, which is not always the case, especially for new mechanisms. In addition, it is not understood, in which way AEs should be included when planning subsequent dose levels. When planning a FIH, trial experience on AEs does not exist. Thus, the AE part of this statement should be removed. **Proposed change:** The choice of the subsequent dose levels should include some estimate of the exposure levels and whenever possible potential PD effects to be achieved.	Not accepted. Focus is on safety and monitoring for adverse events.
390-391	51	**Proposed change:** The choice of subsequent dose levels should include some estimate of the potential nature and duration of PD effects and	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		exposure levels to be achieved as well as adverse effects seen (if any).	
391	40	**Comments:** I am not sure it is always possible to provide an estimate of potential PD effects at the dose levels prior to the study starts. Eg. PD effects to be studied in humans may not have been studied pre-clinically. Clarification needed between preclinical information (PD or biomarker effect, AE seen,…) and emerging clinical data.	Not accepted. Too specific detail.
391-396	16	**Comments:** Are there recommendations for changes in sample sizes as doses are escalated? For example, start with 4 (3 drug, 1 placebo) subjects and then increase in sample size as therapeutic doses are achieved.	Not accepted. Too specific detail.
392-394	30	**Comments:** This section should more explicitly state that both PK and PD data from the emerging clinical studies should be incorporated into dose escalation decisions, not just clinical data from an unspecific cohort. **Proposed change:** The dose increment between two dose levels should be guided by the dose/exposure-toxicity or the dose/exposure-effect relationship defined in non-clinical studies and by all emerging clinical and pharmacological data, including that from the immediately previous dose cohort and later time points from earlier cohorts.	Partly accepted. Text amended.
392-394	41	**Comments:** The emerging data referred to here should include PK and PD data, and should always include data from the immediately previous cohort. The dose should only be escalated by an increment that is justified by this data.	Partly accepted. Text amended.
394	47	**Comments:**	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		The word toxicity should not be used parallel to intolerability. **Proposed change:** Suggest changing: 'dose/toxicity or dose/effect' to 'dose/toxicity or dose-effect/tolerability'	detail.
394-395	22	**Comments:** Suggest defining high-dose and low-dose increment more precisely. **Proposed change:** Please consider 5 fold increment below ATD and 3 fold increment above ATD, and a decrease of increment to less than 3 fold when conditions in line 394-395 are met	Not accepted. Too specific detail.
396	13	**Minor text comment:** We propose to change "*Should be selected*" to "*to be selected*" OR "*that should be selected*".	Partly accepted. Text amended.
396-399	3	**Comments:** In respect of dose escalation, the EMA Guidance rightly highlights non-linear PK and the reliability with which potential adverse effects can be monitored in humans before they escalate into something serious/irreversible (lines 396-399).	General agreement.
397	14	**Comments:** "…before they escalate into **something** serious/irreversible." **Proposed change:** "…before serious/irreversible effects result."	Partly accepted. Text amended.
398	5	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		This line states 'when non-linear PK, should be considered', but this is not very specific. **Proposed change:** 'when non-linear PK, smaller dose increments should be implemented'.	Text amended.
398	17	**Comments:** 'Non-linear PK' includes situations where exposure increases less than proportionally with dose. For the avoidance of doubt, please clarify. **Proposed change:** Evidence of non-linear PK **(increase in dose leads to greater increase in exposure than would be predicted from a linear relationship)**, smaller…	Partly accepted. Text amended.
398	22	**Comments:** The below sentence is poorly worded as non-linearity might be of 2 types. In addition saturation of absorption should not prompt decreases in the dose steps. "Furthermore, if there is evidence of non-linear PK, smaller dose increments, particularly in the later parts of SAD/MAD, should be considered." **Proposed change:** Consider rewording.	Partly accepted. Text amended.
398	35 *confidential*	**Comments:** Further, if there is evidence of non-linear PK, smaller dose increments, particularly in the latter parts of SAD/MAD, should be considered.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Consider choosing an alternate phrase for “non-linear PK”. Suggest using “more than proportional increase in PK with increase in dose”. Non-linear PK can either be more than proportional increase in systemic exposure to increase in the dose or less than proportional increase. The implicit assumption in the current context is more than proportional increase and it makes sense to consider smaller than usual dose increments. On the other hand, if a less than proportional increase in exposure with increase in dose is observed, then the value of continuing on the pre-specified dose escalation strategy as well as max dose may need to be reconsidered.	
398	47	**Comments:** Can “non-linear PK” be further clarified? For small molecules, non-linear PK probably refers to “more than dose-proportional exposure”, in which case a measure to take smaller increments is well understood. That may not necessarily hold in the same way for biologics, e.g. if one aims to achieve complete binding, but has to go by smaller increments, that may make the study much longer.	Partly accepted. Text amended.
398-399	10	**Comments:** Non-linear PK can result in a lower or higher than dose proportional increase of exposure. **Proposed change:** Specify that smaller dose increments should be considered in case of higher than dose proportional increase of exposure.	Partly accepted. Text amended.
398-399	33	**Comments:** Non-linear PK can result in a lower or higher than dose proportional increase of exposure. **Proposed change:** Specify that smaller dose increments should be considered in case of higher than dose proportional increase of exposure.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
398-399	47	"…if there is evidence of non-linear PK, smaller dose increments, particularly in the later parts of SAD/MAD, should be considered." **Comments:** Only true for "supra-proportional" non-linear PK. Would not apply for "sub-proportional" non-linear PK. Suggest to modify to, "if there is evidence of supra-proportional non-linear PK" **Proposed change** Furthermore, if there is evidence of non-linear supra proportional PK, smaller dose increments, particularly in the later 398 parts of SAD/MAD, should be considered.	Partly accepted. Text amended.
399	22	**Comments:** The “significant difference” is a statistical term which is not quantified and remains somewhat vague. **Proposed change:** Suggest replacing “significant” by “substantial”. Significance refers to a statistical test. Suggest that applicants should define in the protocol quantitatively what is considered a substantial difference	Partly accepted. Text amended.
399	30	**Comment:** This advice could be strengthened by changing ‘considered’ to ‘used’ and clarification of that higher blood (not lower) concentrations are important. **Proposed change:** Furthermore, if there is evidence of non-linear PK with higher blood concentrations that expected, smaller dose increments should be used.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
399-402	41	**Comments:** Again, the data to be taken into account here should include PK and PD data as well as clinical data.	Partly accepted. Text amended.
399-402	46	**Comments:** The real action to take is the adjustment of the doses, not the substantial amendment which is a way to do it. **Proposed change:** "If emerging clinical data..., adjustment of the planned doses would be necessary, which may require a susbtantial amendment unless this possibility ..."	Partly accepted. Text amended.
399-402	47	**Comments:** “If emerging clinical data reveal significant differences….” As long as we are within the exposure limits, there shouldn’t be any need for a substantial amendment that may unnecessary prolong the clinical trial. **Proposed change:** If emerging clinical data reveal significant differences from non-clinical or modelling and simulation data, a substantial amendment may be required to adjust planned dose levels unless this possibility was discussed including predefined decision criteria and approved in the protocol the dose for the next cohort should be adjusted based on PK data.	Partly accepted. Text amended.
399-402	51	**Comments:** If doses are planned and not fixed in the protocol why would there be a need for protocol amendment? As long as there are exposure based stopping criteria and limited steps in between dose escalation, flexibility is there not to have a protocol amendment.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: If emerging clinical data reveal significant differences from non-clinical or modelling and simulation data, a substantial amendment may be required to adjust the study design/conduct (the adjustment in relation to the planned dose levels) ~~unless this possibility was~~ should have been discussed including predefined decision criteria and approved in the protocol.	
399-402, 403-404	3	**Comments:** The second (lines 399-402) is: "If emerging clinical data reveal significant differences from non-clinical or modelling and simulation data, a substantial amendment may be required to adjust planned dose levels – unless this possibility was discussed including predefined decision criteria and approved in the protocol". The third refers to dose skipping (lines 403-404).	Partly accepted. Text amended.
399-402	16	**Comments:** The guidance is vague regarding criteria for dose escalation and subject cohort size during escalation; for example, how will the escalation change from a drug with linear PK vs. non-linear PK? Can the guidance include an example?	Partly accepted. Text amended.
399-402	17	**Comments:** This section states that it is acceptable to specify in the protocol dose decision criteria that apply if pre-specified dose levels need to be adjusted. Given the difficulty in reliably predicting exposure in humans from animal data, pre-specification of dose selection criteria should be allowed as an *alternative* approach to specifying planned dose levels and exposures, as well as an approach to adjusting them. **Proposed change:** Please add: If all dose levels and exposures are not pre-specified in the protocol, and dose selection is guided by pre-specified criteria, a substantial amendment will be required to make any significant change to the dose selection criteria.	Partly accepted. Text amended.
399-	18	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
402		It is possible that, during the conduct of the study, emerging clinical data may not be as predicted from the non-clinical or modelling and simulation data. However, as long as the pre-determined criteria for dose escalation and stopping have not been met, there should be no requirement for a substantial amendment. However, if the emerging data warrant changes to the pre-determined escalation criteria, then a substantial amendment would be needed. **Proposed change:** From If emerging clinical data reveal significant differences from non-clinical or modelling and simulation data, a substantial amendment may be required to adjust planned dose levels unless this possibility was discussed including predefined decision criteria and approved in the protocol. To If emerging clinical data reveal significant differences from non-clinical or modelling and simulation data, resulting in the need to change pre-determined criteria such as dose escalation or maximum exposure, a substantial amendment may be required unless this possibility was discussed including predefined decision criteria and approved in the protocol.	Text amended.
399-402	30	**Comments:** It should not be just clinical data that should be compared to non-clinical data but also the emerging PK, PD and safety data. **Proposed change:** If emerging PK, PD or safety data reveal significant differences from non-clinical or modelling and simulation data, …	Partly accepted. Text amended.
400	10	**Comments:** Substantial amendments should be required only if a dose adjustment exceeds the originally approved dose range (i.e. PK increases lower than dose-proportional). Risk-based reduction of originally planned dose steps should be possible without	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		a substantial amendment. **Proposed change:** Specify the need for a substantial amendment	
401	53	**Comments:** evasive wording "… was *discussed* including…" **Proposed change:** "… was adequately described including…	Partly accepted. Text amended.
402	14	**Comments:** "…approved in the protocol." This is unclear; "approved" by whom? "in the approved protocol" ? Please clarify.	Partly accepted. Text amended.
402-403	10	**Comments:** Skipping of a dose may be acceptable without a substantial amendment if conditions pre-defined in the protocol are met, e.g. an unexpected shallow dose-exposure or exposure-response relationship. **Proposed change:** At the end of the sentence in line 404, it should be added "unless pre-specified in the protocol".	Partly accepted. Text amended.
403	47	**Comment 1:** Overall, the draft CHMP Guidance is too prescriptive as to what constitutes grounds for a substantial amendment of a FiH study protocol, whereas some of the decisions to implement changes to dose escalation on the basis of emerging safety and PK data may be pre-specified in the original protocol. This may include the decision to skip a dose provided the	Partly accepted. Text amended.

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		criteria to inform this decision were specified in the original protocol. **Comment 2:** Depending on the behaviour of the compound in man dose skipping may be predefined. If for example for the FiH dose to a HV it is unclear if the PK of the compound follows a specific animal species or not, various dedicated approaches for dose escalation may be pre-specified in the protocol depending on the first PK data in humans. **Proposed change:** "Any dose skipping should take aspects such as steepness of dose-response curve or saturation of target into account and requires a substantial amendment **unless this possibility was discussed including predefined decision criteria and approved in the protocol**".	
403-404	20	**Comments:** The draft text which currently states that any dose skipping requires a substantial amendment is not consistent with some widely used approaches for single dose escalation studies in patients, especially for oncology patients. Dose skipping is a standard element of some Single Ascending Dose (SAD) statistical algorithms such as the continual reassessment method (MRM) or modified CRM. A more appropriate rule would require a substantial amendment for any departure from the prospectively specified rules governing dose escalation, as outlined in other sections of the document. This is in relation to patient studies only and not healthy volunteer studies.	Partly accepted. Text amended.
403-404	21	**Comments:** The term "dose skipping" is difficult to understand, also in the context of adaptive protocols, where usually doses are not pre-defined (and can therefore not the "skipped"); dose escalation limits are set by maximum dose increments. **Proposed change:** Please could you clarify?	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
403-404	22	**Comments:** Suggest adding to the guideline the following wording regarding dose skipping. **Proposed change:** "…unless the possibility was discussed in the predefined dose escalation criteria"	Partly accepted. Text amended.
403-404	33	**Comments:** A dose skipping following the observation of a much lower exposure than expected should not require a substantial amendment, provided it is pre-specified with the appropriate rationale and rules in the protocol.	Partly accepted. Text amended.
403-404	39	**Comments:** In case of much lower exposure than expected, skipping dose should be possible without amendment, as soon as it is pre-specified with the appropriate rationale and rules in the protocol.	Partly accepted. Text amended.
403-404	40	**Comments:** Any dose skipping does not require systematically an amendment. Indeed, an amendment is not relevant for an adaptive design used in oncology, such as CRM, which predefine in the protocol the rules for dose skipping. **Proposed change:** "Any dose skipping should take aspects such as… and required a substantial amendment *if not already specified in the protocol*."	Partly accepted. Text amended.
403-404	47	**Comments:** Historically, many Phase I protocols defined specific dose levels for each cohort without flexibility. In recent years adaptability has been incorporated within Phase 1 protocols where "anticipated" dose levels are given for each cohort but with the flexibility to deviate from the planned dose levels based on exposure (PK), especially for oncology patients. Dose	Partly accepted. Text amended.

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		skipping is a standard element of some Single Ascending Dose (SAD) statistical algorithms such as the continual reassessment method (MRM) or modified CRM. A more appropriate rule would require a substantial amendment for any departure from the prospectively specified rules governing dose escalation, as outlined in other sections of the document. This is in relation to patient studies only and not healthy volunteer studies.. Since the guidance indicates the protocol specify the number of cohorts and a maximum dose/exposure, a substantial amendment should not be required to adjust exposures within these limits. The protocol could include language that the fold increase from one cohort to the next does not exceed a specified increase (e.g. 3 fold the previous dose). **Proposed change:** Clarify that the term “dose skipping” applies only when pre-specified dose levels are provided without the flexibility to alter doses within the protocol as per line 421-422. Dose “skipping” should be permitted without a substantial amendment when based on emerging exposure (PK) data and within the predefined maximums defined in the protocol.	
403-404	47	**Comments:** Bayesian approaches to FIH study design are becoming more prevalent. One such approach used a Bayesian Logistic Regression Model to predict toxicity at the next dose level based on the previous clinical data. In these models there is the possibility for dose level skipping and/or intermediate dose levels between those specified in the protocol to be recommended by the model. The utilizing such dose skipping and/or use of non-specified dose levels should be included in the guideline, as well as the considerations to be evaluated when determining the suitability in an individual case.	Partly accepted. Text amended.
404	46	**Comments:** In practice, "dose skipping" in my experience would only be discussed if observed exposure in humans is much lower than predicted based on animal data : this could be clarified here.	Partly accepted. Text amended.
405-433,	16	**Comments:** Is there guidance on performing exposure-response (safety) analyses prior to escalating dose or going to MAD?	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			detail.
405-433,	20	**Comments:** We suggest referring to ICH-M3(R2) and ICH-S9 (oncology) guidance documents, which provide recommendations as to how the NOAEL exposures can guide highest dose for non-oncology and oncology indications.	Partly accepted. These are included in the references in section 3.
405-433,	20	**Comments:** The uncertainty in translating “plateauing” exposure or maximum enzyme inhibition from nonclinical to human should be considered to allow flexibility in setting the maximum exposure target. In order to estimate “plateau” or Emax with high precision at the end of study, it may be necessary to have data from higher exposure a few fold above Emax to estimate Emax. Please also clarify that stopping criteria are informed by nonclinical data, but the most appropriate approach is an integrated risk assessment that takes into account the totality of data – which includes emerging clinical data that is not available at the time of CTA submission. As discussed above regarding flexibility for dose escalation (Lines 345-350), flexibility to move from SAD to MAD should not be prevented when safe to do so and rules properly pre-specified and justified in the protocol. It should be made clear that a substantial amendment is only required if pre-specified limits set in the initial protocol are altered. **Proposed change:** For integrated protocols, where it may not be possible to predefine definite doses in all study parts, a clear statement should be included that the doses will be chosen based on predefined (dose selection) criteria to permit a Sponsor to move between the stages of the protocol without the need for a substantial amendment. These criteria should integrate data from previous study parts once these are completed and should not exceed the maximum exposure unless justified	Partly accepted. Text amended.

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		by the sponsor when requesting a substantial amendment (see also stopping criteria in section 8.2.10). If an absolute maximum dose cannot be provided, then this should be justified and the maximum fold- increase in dose or exposure from one cohort to the next should be clearly stated as well as a maximum number of cohorts to be evaluated. A maximum exposure limit would be expected in this situation. If any of the above limits cannot be clearly justified, substantial amendments will be required to move to the next stage of the protocol.	
405-433,	20	**Comments:** This section needs to be reworded to focus on exposure and not dose. A maximal exposure limit should be clearly stated in the protocol with justification. It is very difficult to convert this to statements around dose with any confidence when the variability in the PK is not yet known in humans and the dose exposure relationship is being estimated from animal data. To put a maximal dose into the protocol will result in unnecessary major amendments. 7.4 is also particularly problematic for immunotherapy biologics, where a maximum dose set based on serum levels determined in human PK studies would not necessarily reflect tumor concentrations of the drug, when in many case the effects are expected to mediate by activity on tumor infiltrating immune cells, or targets preferentially expressed in the tumor microenvironment. It is therefore difficult to set a maximum dose based on these factors, and the highest dose studied will generally need to be based on a combination of PD hypotheses, clinical safety from previous doses tested, and emerging clinical activity since these trials are conducted in patients. We continue to believe that oncology products should remain out of scope for this revised guidance.	Partly accepted. Text amended.
405-433,	21	**Comments:** We suggest focussing on maximum exposure for FIH trials and consecutive parts in an integrated early phase protocols, rather than on maximum dose in this section, for the reasons outlined above. The permitted maximum (mean and individual) exposures usually guide the determination of the maximum doses/dosing regimens. Exposure should not be	Partly accepted. Text amended.

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		seen as the second best option “if an absolute maximum dose cannot be provided”. **Proposed change:** To amend the text as follows: “In addition, if non-clinical data or modelling data indicate a plateauing of exposure, this should be taken into account **for the ongoing dose/dosing regimen selection during a trial, regardless whether the increasing of doses is viewed as a safety concern.”** To amend the text as follows: “~~If an absolute maximum dose cannot be provided, then this should be justified and~~ **The maximum exposure (mean and individual) and** the maximum fold-increase in dose from one cohort to the next should be clearly stated as well as the maximum number of cohorts to be used. **The use of an absolute maximum dose rather than exposure should be justified.**”	
405-433	47	**Comments:** At the stage of entry into human, the expected human therapeutic dose is hypothetical, i.e., the expected therapeutic exposures are only projections and frequently need to be revised in the course of clinical development. Therefore, there is a risk of limiting dose-escalation in the absence of dose-limiting toxicity. Provided that toxicities are monitorable, reversible, and clinically manageable and thereby in alignment with ICH M3(R2), there are multiple reasons for exploring high exposures, i.e., above the NOAEL. 1) High exposures may be required to detect efficacy: although nonclinical efficacy models and other predictive models (e.g., PKPD models) provide an estimate of the expected therapeutic dose, the true clinically efficacious dose is not determined until later in development. 2) In some therapeutic areas, patients may intentionally or unintentionally take doses that exceed their prescribed dose	Partly accepted. Text amended.

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		in the post-marketing setting (e.g., pain); thus, exploring exposures that might exceed the predicted therapeutic dose can support continued development and effective safety monitoring in future studies. 3) Phase I units offer the opportunity for unique or intensive monitoring capabilities that other settings cannot, and Sponsors should capitalize on this opportunity. The recommendation to limit testing above the NOAEL could have the unintended effect of simply shifting risk to more vulnerable populations or less well-monitored patients, which could lead to an even greater public health risk. 4) Once a drug enters late stage development or the post-approval setting, patients with altered metabolism or clearance (e.g., due to renal, hepatic, or other disease) may be unintentionally exposed to high levels; by understanding drug effects at these higher exposures, the safety monitoring plan can be better informed and can reduce potential harm. Careful exploration of potentially supra-therapeutic doses in healthy volunteers (who have greater physiologic reserve) is essential in order get adequate coverage in a less vulnerable population, and in a carefully monitored and controlled setting, to account for potential PK or PD variability that may occur later in development or in the marketed population post-approval, where the number of people exposed may be greater and the monitoring less stringent, or to account for overdoses or extra-dosing, or to explore the steepness of the dose response curve. 5) Collecting safety data at exposures above the therapeutic level enables the collection of QTc data at supratherapeutic doses (as required by ICH E-14 which states: “An adequate drug development programme should ensure that the dose-response and generally the concentration-response relationship for QT/QTc prolongation have been characterized, including exploration of concentrations that are higher than those achieved following the anticipated therapeutic doses.”). Ultimately, understanding the effects of supratherapeutic exposures can help derisk a compound and protect patients. Furthermore, this requirement is likely to have major impacts on feasibility of early phase studies conducted in the EU. In combination with the requirement to submit a major protocol amendment in order to explore exposures higher than the upper limit of the predicted therapeutic range, irrespective of clinical data collected previously and irrespective of	

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		target biology and predicted toxicities, imposes undue burdens and is not scientifically driven. We would suggest re-wording to explain that doses above the expected human therapeutic dose (if known) may need to be studied in healthy volunteers in a carefully controlled and well-monitored fashion, but at a reasonable multiple of the expected therapeutic exposure justified to provide adequate coverage for PK or PD variability in the population or meet other regulatory expectations (e.g., TQT) unless scientifically justified. Of course the usual stopping criteria would need to be justified and the intent should not be to define MTD. Specific examples that would be considered "scientifically justified" would be very helpful. Entry into human protocols should specific a top exposure to be tested; however, this should not always correspond to the expected therapeutic exposure for the reasons above. A substantial protocol amendment would then be needed to explore higher exposures than specified in the initial protocol. **MTD in healthy volunteer trials -** "A trial design using a MTD approach is considered to be unethical for healthy volunteers." There are at least two potential problems with this statement: 1) The term "MTD approach" is vague and open to multiple interpretations. Some might interpret this to mean that no further escalation could occur after a cohort with any AEs or tolerability issues, no matter how minor. The term "MTD approach" should be defined or restated to clarify what is meant by such an approach. Certainly, we do not condone blindly increasing dose until lack of tolerability is encountered. The modern approach is to attempt to characterize the safety of a compound via careful dose exploration, which should include, where possible, doses well above the targeted efficacious dose. As we have discussed above, Phase 1 is the best opportunity to explore effects of supratherapeutic exposures in a controlled environment that may be used subsequently to predict response to drug-drug interactions, special populations, and overdose situations. 2) Healthy volunteers are not the only group for whom an "MTD approach" could be considered unethical. In most cases, even *patient populations* enrolled in Ph1 trials would not be treated for sufficient durations, or at sufficient exposures,	

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		to derive benefit. Hence why would they be treated differently than healthy volunteers with respect to the approach? It is important that throughout the document HV and patients are afforded the same protections and should be treated equivalently in most cases. Scientific, totality of evidence approach would include determination of how MTD is defined, e.g. increases in liver enzymes excluding liver histopathology, could define an MTD. However, this could also be a pharmacological effect and liver enzymes can be readily monitored in the clinic. This could lead to, for example, liver enzymes increasing which could be seen as exceeding the MTD. MTD may be determined also by non-severe symptoms such as e.g. nausea, fatigue, or sleep disturbances that do not constitute un-ethical exposure. To this point, the sentence starting on line 429 should safeguard subjects (patients or HV). A further example would be a trial in which healthy volunteers are dosed with increasing doses of an incretins class molecule (GLP-1) until nausea is found. This represents a well characterized, monitorable, reversible, toxicology based finding that could be interpreted as an 'MTD approach.' **Proposed language:** **"Determination of maximum dose for phase 1 studies should be based on the overall risk assessment of the compound (e.g. steepness of the dose / exposure response curve, specific risks related to the MoA or off-target effects etc.), the toxicology findings, and its available nonclinical and clinical PK/PD data.** **When supported by toxicology studies and clinical safety monitoring, maximum dose may exceed NOAEL, and doses that achieve near maximum PD effects** **Excessive exposure multiples beyond maximum PD effects should be avoided, unless justified by scientific necessity and adequate safety monitoring plan.** **In some circumstances, based on the totality of evidence of risk for healthy subjects, the achievement of a MTD may be a reasonable objective in this population."**	

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405-433	47	**Comments:** This section is problematic for immunotherapy biologics in particular. A maximum dose set based on serum levels determined in human PK studies would not necessarily reflect tumor concentrations of the drug, when in many case the effects are expected to mediate by activity on tumor infiltrating immune cells, or targets preferentially expressed in the tumor microenvironment. It is therefore difficult to set a maximum dose based on these factors, and the highest dose studied will generally need to be based on a combination of PD hypotheses, clinical safety from previous doses tested, and emerging clinical activity since these trials are conducted in patients. While this is briefly touched on in section 7.7 (lines 453-469), further discussion in the guideline of these situations may be helpful.	Partly accepted. Text amended.
405-433	51	**Comments:** This section is problematic for immunotherapy biologics in particular. A maximum dose set based on serum levels determined in human PK studies would not necessarily reflect tumor concentrations of the drug, when in many cases the effects are expected to be mediated by activity on tumor infiltrating immune cells, or targets preferentially expressed in the tumor microenvironment. It is therefore difficult to set a maximum dose based on these factors, and the highest dose studied will generally need to be based on a combination of PD hypotheses, clinical safety from previous doses tested, and emerging clinical activity since these trials are conducted in patients. While this is briefly touched on in section 7.7 (lines 453-469), further discussion in the guideline of these situations may be helpful.	Partly accepted. Text amended.
406	9	**Comments:** Add safety/tolerability and PK evaluation.	Partly accepted. Text amended.
406	30	**Comments:** The pharmacological effects in humans (contrasting with non-clinical studies). This could be emphasised for readers. **Proposed change:** The design of FIH or early CTs often aims to determine a dose or exposure-response curve in humans for the most	Partly accepted. Text amended.

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		relevant pharmacological effect(s), and…	
406-407	47	**Comments:** this is not necessarily correct: the aim often is initially to evaluate safety/tolerability and PK under well-controlled conditions **Proposed change:** Add “safety/tolerability and PK evaluation”, for example “The design of FIH or early CTs often aims to determine a dose or exposure-response curve for the most relevant pharmacological effect(s), safety/tolerability and PK evaluation, and includes a maximum predefined dose or exposure margin.”	Partly accepted. Text amended.
406-408	20	**Comments:** FIH studies and early CTs often do not have clear, validated PD endpoints or biomarkers that can be used to determine exposure-response curves or to define a therapeutic dose. **Proposed change:** “In some cases, depending on the therapeutic target, FIH or early CTs may include PD endpoints or biomarkers that can be used to determine a dose or exposure-response curve for the most relevant pharmacological effect(s). However, regardless of availability of such endpoints, early studies should include a maximum predefined dose or exposure margin. Deviations from this principle should be justified and may lead to more cautious approaches.”	Partly accepted. Text amended.
406-408	43	**Comments:** For oncology FIH studies with adaptive (Bayesian) model-based design, aiming at determining the MTD or a recommended dose for future use in patients, defining a maximum dose and/or maximum exposure in advance should not be required. Clarification would be necessary as it is not apparent if such studies are considered as deviation by default or if this	Partly accepted. Text amended.

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		requirement applies only to HV studies.	
406-408	47	**Comment:** It is unclear whether this statement should be ".. predefined dose or exposure margin" or " predefined dose or exposure"?	Partly accepted. Text amended.
406-408	51	**Proposed change:** The design of FIH or early CTs often aims to determine a dose or exposure-response curve for the most relevant pharmacological effect(s), and includes a maximum predefined dose or exposure ~~margin~~.	Partly accepted. Text amended.
407	9	**Comments:** Better to refer to maximal exposures by default unless this is impossible for any reason	Partly accepted. Text amended.
409	22	**Comments:** See proposed change. **Proposed change:** Suggest to change to "a maximum dose **or** exposure or **both**"	Partly accepted. Text amended.
409	47	**Comments:** Consideration should be given to amending the text to ensure different methods of administration are covered. **Proposed change:** "A maximum dose, including consideration of relative systemic maximum exposures, which should not be exceeded…."	Partly accepted. Text amended.
409-	46	**Comments:**	Partly accepted.

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410		Exposure is an outcome variable so if an exposure exceed the defined max exposure this would be prior to the possibility of submitting/approving a substantial amendment. Or is it meant a substantial amendment for the next dose groups? To clarify. For a FIM study, as the recommendation is to obtain human PK during the study, it seems that only a maximum exposure should be needed to drive the conduct of the study. Once we have PK, a maximum dose becomes useless.	Text amended.
409-411, 416-423	3	**Comments:** In summary, the EMA Guidance reiterates (lines 409-411) that: "A maximum dose or exposure, which should not be exceeded in the study without approval of a substantial amendment, should be pre-defined and justified in the protocol for the full CT and/or each study part." See also (lines 416-420) for application to integrated protocols as, alternatively and unusually (lines 421-423), a maximum-fold increase in dose from one cohort to the next and maximum exposure limit need to be pre-specified.	Partly accepted. Text amended.
409-411	16	**Comments:** Should some of these discussions about a maximum dose or exposure occur with the EMA prior to escalating?	Not accepted. Too specific detail.
409-411	51	**Proposed change:** A maximum dose ~~or~~ <u>based on a maximum</u> exposure, which should not be exceeded in the study without approval of a substantial amendment, should be pre-defined and justified in the protocol for the full CT and/or each Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products study part.	Partly accepted. Text amended.
412-415	22	**Comments:** This whole sentence is unclear. Suggest revision of wording.	Partly accepted. Text amended.
413-	47	**Comments:**	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
427		The uncertainty in translating “plateauing” exposure or maximum enzyme inhibition from nonclinical to human should be considered to allow flexibility in setting the maximum exposure target. In order to estimate “plateau” or Emax with high precision at the end of study, it may be necessary to have data from higher exposure a few fold above Emax to estimate Emax. **Proposed change:** Add consideration for between-species translational uncertainty. Add clarification that “MTD” can only be estimated (not observed) after a robust dose-exposure-response relationship for the tolerability event has been established over a wide dose range to estimate with accuracy.	detail.
413-414	47	**Comments:** The second part of the sentence is considered unclear and should be deleted. If the exposure of a drug is plateauing i.e. the exposure will not increase anymore when escalating dose, increasing of doses should not add safety concerns. Still, any further increase of dose does not make any sense and therefore should require stop of dose escalation. A related stopping rule might be considered in the study protocol. **Proposed change:** In addition, if non-clinical data or modelling data indicate plateauing of exposure, this should be taken into account for the defined maximum dose~~, regardless as to whether increasing of doses is viewed as a safety concern~~.	Partly accepted. Text amended.
416-420	24	**Comments:** Integrated protocols should indicate clearly the criteria to progress from one study section to the following one. It should be clearly stated that such sections cannot be contemporaneous.	Partly accepted. Text amended.
416-422, 435-	47	**Comments:** Sponsor flexibility to move from SAD to MAD should not be prevented when safe to do so and rules properly pre-specified	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
439, 495-496, 497-499; 626-628, 677, 634-636		& justified in the protocol. It should be made clear that a substantial amendment is only required if pre-specified limits set in the initial protocol are altered. **Proposed change:** For integrated protocols, where it may not be possible to predefine definite doses in all study parts, a clear statement should be included that the doses will be chosen based on predefined (dose selection) criteria to permit a Sponsor to move between the stages of the protocol without the need for a substantial amendment. These criteria should integrate data from previous study parts once these are completed and should not exceed the maximum exposure unless justified by the sponsor when requesting a substantial amendment (see also stopping criteria in section 8.2.10). If an absolute maximum dose cannot be provided, then this should be justified and the maximum fold- increase in dose or exposure from one cohort to the next should be clearly stated as well as a maximum number of cohorts to be evaluated. A maximum exposure limit would be expected in this situation. ~~In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified~~. **The maximum exposure in studies with healthy volunteers should not only cover the anticipated therapeutic dose range but also an additional predefined adequate safety margin covered by preclinical toxicological and safety pharmacological data to account for variability in patient population introduced by eg DDIs, organ failure or accidental overdose.**If any of the above limits cannot be clearly justified, substantial amendments will be required to move to the next stage of the protocol.	
418	30	**Comments:** This should indicate that all previous study parts should be considered. There is no need to state 'once these are completed' since this may permit going ahead with the study without considering these data if that study part is not completed. These words can simply be deleted. **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		These criteria should integrate data from all previous study parts, including all follow up data, and …	
421	13	**Comments:** It is not clear to what the absolute maximum dose refers to. **Proposed change:** Please clarify. Moreover, please add "*If one dose level is not tolerated, a lower dose level should be selected.".*	Partly accepted. Text amended.
421-423	43	**Comments:** While the maximum fold-increase can be pre-defined in oncology FIH studies, the maximum number of cohorts as well as a maximum exposure limit cannot.	Partly accepted. Text amended.
421-423	47	**Comments:** When the maximum expected exposure is provided in the protocol, can the fold of increase in dose from one cohort to the next and the maximum numbers of cohorts to evaluated be flexible, if the dose escalation will be guided based on the shape of the PK/PD response curve? Criterion will be included in the protocol, but the value of fold and cohort numbers may not be specified in this case.	Partly accepted. Text amended.
424	25	**Comments:** It is usually required exploring the safety ofsupratherapeutic dose(s) in Phase 1 First in Human trials. These safe supra-therapeutic dose levels are important to estimate the impact of supra-therapeutic exposure in patients and to eventually guide healthcare professionals in case of supratherapeutic exposure (e.g. due to drug interaction, overdosage, change in clearance of the drug due to liver or renal impairment). Supratherapeutic dose(s) will also be required to evaluate the potential effect of the investigational product on QT interval which is now suggested in phase 1 studies (Refer to ICH E14 Q&As (R3))	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
424-425	9	**Comments:** This is very restrictive. It is probably better to investigate higher (supratherapeutic levels) under controlled circumstances. It is better to know toxicity before going to patients. It may reveal toxicity which prevents further development at an early stage, which is positive.	Partly accepted. Text amended.
424-425	12	"*In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified.*" (Section 7.4. Maximum dose and dose range") **Comments:** The therapeutic dose range, although predicted or projected based on nonclinical model data before early clinical trials, often changes during development following emerging clinical efficacy or safety data. Therefore, exploring a wider dose range than the predicted or projected therapeutic dose range in early clinical trials is important for defining a safe and tolerated dose range for future studies. Mainly because early clinical trials are conducted with more intensive safety monitoring compared to later stage studies, they should cover exposure variability in a larger, more diverse patient population, should help to define supra therapeutic dose for thorough QT study) and to determine the PK/PD relationship which narrows down dose range for future studies (minimizing the number of patients exposed to ineffective dose or unsafe dose).	Partly accepted. Text amended.
424-425	14	**Comments:** "In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified." Not agreed; most FIH studies have been conducted with stopping rules allowing escalation beyond NOAEL exposures, and for good reasons. Stopping rules are typically defined to ensure stopping at the appropriate level based on safety and/or reaching some pre-defined pharmacodynamic readout (e.g. full inhibition of an enzyme). Reasons for escalating beyond the "expected human therapeutic dose range" include the need to fully explore safety and	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		tolerability at higher dose, taking intra-subject variability, demographic factors, age, DDIs, organ impairment etc into account. In addition, full characterisation of the pharmacodynamic response may require escalating beyond NOAEL, safety and tolerability permitting. In addition, this requirement runs contrary to the requirement for “supratherapeutic doses” in e.g. TQT studies. Dose levels are constantly varied in the subsequent clinical programme, and the need to increase dose based on emerging clinical data from patients is a common occurrence. A new rule requiring dose escalation to stop in the FIH trial because exposure has reached a value predicted from animal studies will not improve clinical safety; indeed, such a rule will likely require additional safety trials as clinical development progresses and more is learned about the product. The current text includes “unless scientifically justified”, which however reads as an exception. **Proposed change:** Suggest removing the strict requirement for a stopping rule based on animal data and instead focus on stopping rules based on a weight-of-evidence approach, including emerging data from the FIH trial, animal safety data, animal pharmacology and mechanism of action of the product. See comment above regarding the proposed requirement for a substantial amendment to escalate beyond NOAEL.	
424-425	17	**Comments:** The expected therapeutic dose range is often not defined reliably during early clinical trials, so we don’t know with confidence what therapeutic exposure is. PD measures in healthy volunteers may not predict therapeutic exposure in patients. A margin is required to gather data at the higher plasma concentrations that might occur (or be needed) in patients. Also, in high precision QT studies that are done early in clinical development, supra-therapeutic exposure must be tested. **Proposed change:** Delete lines 424–425.	Partly accepted. Text amended.

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424-425	20	**Comments:** Please clarify if this is suggesting to stop at the therapeutic range in the SAD in healthy subjects, and explore higher exposure range in the rest of the SAD and MAD cohorts in patients. What about the DDI and QT studies that might result in supra-therapeutic range, do all these study required to be conducted in patient population? What if conducting these supra-therapeutic studies is not practical in the patient population?	Partly accepted. Text amended.
424-425	21	**Comments:** In exploratory FIH and early phase trials it may be justified to exceed the expected human therapeutic dose range if no toxicity/stopping rules are met. This may be required to establish supratherapeutic exposures for the evaluation of cardiac safety, drug-drug-interactions, and to cover clinical and overdose situations. **Proposed change:** To amend the text as follows: "In general, the exposure at the human therapeutic dose range **should provide a framework for exposures to be explored** in **trials** in healthy volunteers**. If exposures beyond the therapeutic range are to be explored in these trials, justification should be provided in the CT protocol."**	Partly accepted. Text amended.
424-425	22	**Comments:** "In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified." This statement is considered to be in contrast to the nature of early clinical development, i.e. to explore the dose/exposure-effect relationship with special attention to safety. The expected therapeutic human dose range may not always be known and cannot be confirmed with certainty in such an early phase of development. Additionally, it is required to explore safety implications of increased exposure, to understand risks in DDI and thorough QT studies, where	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		supra therapeutic dose are either expected or required. **Proposed change:** Suggest to delete this statement	
424-425	23	**Comments:** Referring to our comments on lines 364-373, it is considered important to be able to explore the full safety range in early development under strictly controlled Phase I conditions. **Proposed change:** "In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified. **Examples of scientific justification may include a well-tolerated drug where the pharmacodynamic Cmax has not been achieved or the drug is well tolerated in the absence of a marker of biological effect.**"	Partly accepted. Text amended.
424-425	26	**Comments:** Limiting the exposure to the (plateau?) of the expected human therapeutic dose range in healthy volunteers may significantly limit the value of a FIH study. There is no need, and it is not ethical, to proceed to exposures far beyond the plateau of the therapeutic response, ACRO considers that dosing up to 5-10 fold above this anticipated plateau should be allowed if there are no further toxicity concerns since 1) the PD in healthy volunteers cannot always be measured, 2) the exposure-PD relationship in healthy volunteers can be different in patients, 3) supratherapeutic dose levels are needed to reliably detect human toxicity, especially in a limited number of subjects, and to use for instance Concentration Effect Modelling for QTc evaluation according to the ICH-E14 Q&A revision. Similarly, target saturation should be taken into account but a safety margin beyond maximum target saturation (and therapeutic effect) should be assessed. **Proposed change:**	Partly accepted. Text amended.

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		Revise the sentence to read: “The range of exposure at the expected human therapeutic dose range should be scientifically justified. Similarly, target saturation should be taken into account but a safety margin beyond maximum target saturation (and therapeutic effect) should be assessed.”	
424-425	27	**Comments:** Many preclinical efficacy models are limited in their ability to accurately predict the human therapeutic dose range. Furthermore, due to intersubject pharmacokinetic variability, sponsors may need to dose across a broader range in order to ensure that all subjects achieve the minimum anticipated exposure in the therapeutic dose range. There is therefore a critical need to safety explore potential drug activity above the predicted therapeutic exposure range, when enabled by preclinical safety studies. This can be achieved effectively and safely, especially when guided by demonstration of pharmacodynamic engagement, with careful clinical monitoring, and with prudent dose escalation. **Proposed change:** In general, the exposure at the expected human therapeutic dose range should be one of the factors considered in determining the maximum dose, in context of the safety profile and evidence of target engagement.	Partly accepted. Text amended.
424-425	29	**Comments:** “In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified.” The therapeutic dose range is predicted based on pre-clinical information. As the PK and PD variability in humans in unknown/uncertain, there will be significant uncertainty regarding the true therapeutic dose range in humans. Consequently it would be reasonable to explore exposures above the predicted therapeutic dose range in order to cover potential exposure in special population, DDI etc. during this well controlled clinical setting. For example, it has been usual in a SAD and to some degree in a MAD study to exceed the anticipated maximum therapeutic exposure in order to gain in a controlled environment safety information to cover the greater variability in exposure in a patient population e.g. as a consequence of renal or hepatic impairment and to some degree potential DDI situations and also to gain	Partly accepted. Text amended.

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		information on QT effects at a supratherapeutic dose (using concentration effects modelling in these studies) or to define a supratherapeutic dose for a standalone TQT study. Nevertheless, for these purposes, the aim should to explore likely supra therapeutic exposures that may arise in normal clinical circumstances but without deliberately reaching poorly tolerated or toxic levels. If poorly tolerated or toxic exposures may be reached, the supra therapeutic exposures require significant scientific justification. The same applies to FTIM studies in patient volunteers when supra therapeutic exposures are planned. **Proposed change:** "In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in volunteers, unless scientifically justified. If it is planned to exceed the therapeutic exposure level predicted by pre-clinical studies, for example to explore potential exposure levels in special populations or caused by DDI, the aim should to explore supratherapeutic exposures that are likely to arise in normal clinical circumstances but without deliberately reaching poorly tolerated or toxic levels. If poorly tolerated or toxic exposures may be reached, the supratherapeutic exposures require significant scientific justification. The same applies to FTIM studies in patient volunteers when supratherapeutic exposures are planned."	
424-425	30	**Comments:** Dosing may sometimes with justification exceed the maximum PD effect so that the effect of modest increases in dose can be established**.** **Proposed change:** While establishing the maximum (well) tolerated dose should not generally comprise an objective of a Phase I study in healthy volunteers; it is usually reasonable to escalate the dose to a level that produces concentrations a little greater than those associated with the maximum desired pharmacodynamic effect. This can provide reassurance that there is a reasonable therapeutic window and that small increases in drug concentrations are unlikely to result in clinically important adverse events. The dose attaining the maximum desired pharmacodynamics effect will only become clear as data	Partly accepted. Text amended.

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		accumulate and are analysed within the FIH study.	
424-425	39	**Comments:** SAD /MAD CT should provide relevant safety and tolerability data with doses beyond the intended therapeutic one, covering potential large population variability and worst case scenario for exposure (Drug-drug interaction, special population with chronic organ failure). This is also aligned with the rationale supporting the supra-therapeutic dose described in the thorough ECG study of ICH E14 guideline. We suggest to introduce this concept of supra-therapeutic exposure based on strong scientific rationale in which simulation from PBPK would be key, and allowing an "X" fold the intended therapeutic exposure. **Proposed change:** In general, the exposure at the expected human therapeutic dose range could be exceeded in studies in healthy volunteers, with the appropriate scientific justification (e.g. potential drug-drug interaction, special population) and pre-specified rules (e.g. not exceeding "X" fold the intended therapeutic exposure) without the intent to reach MTD.	Partly accepted. Text amended.
424-425	40	**Comments:** It states that in general, the exposure at expected therapeutic dose range should not be exceeded in healthy volunteers, unless scientifically justified. However, in my experience, most FIH studies are conducted in healthy volunteers and the higher doses would generally be higher than the expected therapeutic doses, not least to provide additional safety cover. **Proposed change:** Remove the sentence "In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in HV, unless scientifically justified."	Partly accepted. Text amended.
424-425	46	**Comments:** That sentence is a very important one and seems confusing to me : so far, the goal for a FIM study has been to document	Partly accepted. Text amended.

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		safety of "supra-therapeutic" exposures which could be reached in patients due to intrinsic/extrinsic factors (such as DDI) influencing PK. If applied to a FIM study, that sentence should be revisited.	
424-425	47	**Comments:** Healthy volunteer studies are preferred to evaluate supra-therapeutic doses where no particular safety concerns exist, to establish a safety margin prior to exposing the IMP to patients. This is justified often since patients can experience more variable exposures due to for example DDI's. In addition the recent update of ICH E14 guideline allows the use of the FIH study to determine Qtc prolongation, which is typically investigated at supra-therapeutic doses. Note: ICH E14 is not referenced in the 'Legal Basis' (section3). Additionally for a biologic, the estimation of the therapeutic dose and therapeutic dose range can be difficult prior to the first in human study since the dose frequency is important in defining the dose **Proposed change:** Remove: "In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified." Please add a reference to ICH E14 in Section 3.	Partly accepted. Text amended.
424-425	50	**Comments:** We agree that using nonclinical models and simulations to predict the efficacious exposures is important to guide dosing. Significant progress has been made in this discipline. However, we must also realize that such models are imperfect, are not equally predictive in all therapeutic areas, and may not always directly translate to humans. Thus, the predicted efficacious exposure should be used as a guide rather than as a strict limit. At the stage of entry into human, the expected human therapeutic dose is hypothetical, i.e., the expected therapeutic exposures are only projections and frequently need to be revised in the course of clinical development.	Partly accepted. Text amended.

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		The recommendation to not exceed the expected therapeutic dose range in healthy volunteers is potentially problematic. Provided that toxicities are monitorable, reversible, and clinically manageable, there are multiple reasons for carefully exploring high exposures, i.e., exposures that exceed the expected therapeutic range or even may exceed the NOAEL. First, subsequent to the FIH study, e.g., in phase II and beyond, some patients are likely to be exposed to supratherapeutic exposures for a variety of reasons: PK or PD variability, overdose (as often intentionally or unintentionally occurs with pain medications), dosing errors, impaired clearance that may occur with certain diseases, and under other circumstances. Because monitoring is less stringent in studies subsequent to the FIH study, if the clinical effects of such supratherapeutic exposures remain undefined after the FIH study, this recommendation could have the unintended consequence of simply shifting risk to more vulnerable and less well-monitored populations. This could lead to a public health risk. Careful exploration of potentially supra-therapeutic doses in healthy volunteers (who generally have greater physiologic reserve) is therefore important to support continued development and more effective safety monitoring in future studies. It also provides a means to obtain adequate coverage in a less vulnerable population. (Of note, phase I units offer the opportunity for unique or intensive monitoring capabilities that other settings cannot, and Sponsors should capitalize on this opportunity.) Second, high exposures (relative to nonclinical efficacy models) may be required to detect efficacy in the clinic. Although nonclinical efficacy models and other predictive models (e.g., PKPD models) provide an estimate of the expected therapeutic dose, the true clinically efficacious dose is not determined until later in development. Third, this recommendation directly contradicts existing ICH guidance – e.g., ICH E14 which states: “An adequate drug development programme should ensure that the dose-response and generally the concentration-response relationship for QT/QTc prolongation have been characterized, including exploration of concentrations that are higher than those achieved following the anticipated therapeutic doses.”Ultimately, understanding the effects of supratherapeutic exposures can help derisk a compound and protect patients. Importantly, each molecule must be considered on a case-by-case basis, and different limits (higher or lower) may be appropriate in different situations. Furthermore, this is likely to have major impacts on feasibility of early phase studies conducted in the EU. The	

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		requirement to submit a major protocol amendment in order to explore exposures higher than the upper limit of the predicted therapeutic range, irrespective of clinical data collected previously and irrespective of target biology and predicted or observed toxicities, imposes significant challenges. Guidance should be provided on what specific scientific justifications would enable exploration of supratherapeutic exposures in healthy volunteers. **Proposed change:** Lines 424-425: "~~In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified.~~ ***In general, for healthy volunteers confined to a phase I unit where intensive monitoring and quick access to on-site medical care are readily available, exposure at a reasonable multiple above the expected therapeutic dose range (i.e., the exposure range predicted by nonclinical efficacy models) may be carefully explored provided that predicted toxicities are monitorable, reversible, and clinically manageable. For such situations, scientific justification must be clearly provided in the protocol. An example of such a situation would include a small molecule that is being developed for a therapeutic area (such as a CNS indication) where overdose might be expected, where there is considerable uncertainty around the translatability of the nonclinical efficacy model(s), and/or where adequate safety margins exist above the predicted therapeutic dose range.*** ***As with all first-in-human studies, clear stopping criteria should be described, and the intent should not be to find a non-tolerated dose.*** ***Testing of higher exposures than specified in the initial protocol would require a substantial protocol amendment with scientific justification."*** Other specific examples that would be considered "scientifically justified" would be very helpful.	
424-425	51	**Comments:** This portion of the draft guideline does not reflect current practice. Healthy volunteer studies are preferred to evaluate supra-therapeutic doses where no particular safety concerns exist, to establish a safety margin prior to exposing the IMP	Partly accepted. Text amended.

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		to patients. This is justified often since patients can experience more variable exposures (*e.g.,* DDIs for low molecular weight compounds). In addition the recent update of ICH E14 guideline allows the use of the FIH study to determine QTc prolongation, which is typically investigated at supra-therapeutic doses. Finally, for a biologic the estimation of the therapeutic dose and therapeutic dose range can be difficult prior to the first in human study since the dose frequency is important in defining the dose. **Proposed change:** ~~In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified.~~	
424 & 432	9	**Comments:** Data on higher exposure might be needed to have safety data for later studies (DDI, QT, FE). If this is happening in well-controlled situation, guided by interim safety analysis and review meetings, it can be ethically justified? This is the same for patients.	Partly accepted. Text amended.
424-428	10	**Comments:** The main objective of early clinical trials is to investigate the safety and tolerability of an IMP under well controlled conditions. These trials are usually the only ones where detailed data for exposures above the expected human therapeutic dose are collected and thus inform dose-exposure-response models for safety/tolerability endpoints, especially those which are assumed to be mode of action related. The maximum dose / exposure in FIH trials needs to cover the uncertainties of the predicted therapeutic dose / exposure and has to provide a sufficient safety margin with respect to clinical drug-drug-interactions (DDI) and thorough QT investigations. Furthermore, it has to cover variability in exposures for long-term clinical trials in larger patient populations which cannot be as strictly controlled as early clinical trials. Following the guideline's current wording might put patients at later trial stages at higher risk.	Partly accepted. Text amended.

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		Proposed change: Lines 424 and 425 should be deleted. The target saturation aspect should be included in lines 411 – 412: "This justification should be based on all available non-clinical and clinical data, including PD (e.g. target saturation), PK, findings in toxicity studies…".	
424-428	33	**Comments:** The strong wording regarding the limitation of the maximum dose in healthy volunteers is misleading. As requested in several EMA, ICH or FDA guidelines, the maximum dose / exposure in FIH trials needs to cover the uncertainties of the predicted therapeutic dose / exposure (supratherapeutic levels) and has to provide a sufficient safety margin with respect to clinical drug-drug-interactions (DDI) and thorough QT investigations. Furthermore, it has to cover variability in exposures in larger populations which cannot be as strictly controlled as early clinical trials. Following the guideline's current wording might put patients at later trial stages at higher risk (slow metabolizers, variability linked to age, chronic organ failure, disease conditions, weight…). **Proposed change:** In general, the exposure at the expected human therapeutic dose range could be exceeded in studies in healthy volunteers, with the appropriate scientific justification (e.g. PBPK simulation, target saturation…) and pre-specified rules.	Partly accepted. Text amended.
425	34	**Comments:** Please clarify "unless scientifically justified" as the therapeutic dose range is often not well understood. Please provide scenarios where the expected human therapeutic dose range can be exceeded or cannot be exceeded in healthy volunteers.	Partly accepted. Text amended.
426	33	**Comments:** The case of multiple targets is not taken into account.	Partly accepted. Text amended.

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426-428	21	**Comments:** The duration of target saturation and pharmacodynamic effects should also be taken into account, as increase in dose can lead to no increase in target saturation, but increase in duration of action. This may be a desired effect. **Proposed change:** To amend the text as follows: "[…] then the maximum dose/**exposure** should consider when the desired inhibition, **target saturation and duration of action are** achieved and no further therapeutic effect is to be expected by increasing the dose/**exposure**."	Partly accepted. Text amended.
426-428	29	**Comments:** When inhibition by a competitive antagonist is reversible it is never "complete" (ie 100%) but only approaches complete inhibition with increasing concentration. Functionally, the extent of the inhibitory effect will depend also on the concentration of the physiological substrate or (in the case of receptor antagonists) mediator, and this may be much higher than basal levels in relevant pathological circumstances. It may therefore be rational to explore high percent inhibition/ fractional occupancy in specific circumstances. Where relevant, such justification should be explicitly argued. **Proposed change:** "Target saturation should be taken into account, e.g. if the intended therapeutic effect is linked to enzyme inhibition, then the maximum dose should consider when **maximum useful** inhibition is achieved and no further therapeutic effect is to be expected by increasing the dose. **Where maximum useful inhibition approaches 100%, the justification for exploring such high fractional inhibition should be provided**."	Partly accepted. Text amended.
426-428	30	**Comments:** It may not always be possible to measure relevant PD effects directly, if for example the target enzyme is in the brain (as occurred with the Bial trial where a peripheral leukocyte enzyme assay was proposed). If this is the case, then the	Partly accepted. Text amended.

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		consequences of this need to be discussed in this section **Proposed change:** Target saturation should be taken into account, e.g. if the intended therapeutic effect is linked to enzyme inhibition, then the maximum dose should consider when complete inhibition is achieved and no further therapeutic effect is to be expected by increasing the dose. Where measuring this activity is difficult (as for example with CNS target enzymes), then the consequences/implications of this difficulty need to be discussed in the protocol.	
426-428	47	**Comments:** for CNS drugs this is not considered feasible, because the CT will measure concentration of the IMP in blood/plasma/serum, not at the target site (brain). You would not know when, i.e., 100% occupancy is reached in brain. In general, for certain diseases and conditions, even if full target engagement is measured at the target site, it still could be that a higher dose is needed to translate in clinical benefit. **Proposed change:** Target saturation should be taken into account when appropriate,	Accepted. Text amended.
426-428	47	**Comments:** Target saturation at the site of action is often unknown. For example, enzymatic activity measured in leucocytes when the same enzyme is being targeted in the CNS is not clearly relevant to exposures achieved in the CNS. In other words, the leucocyte activity is a surrogate that provides a very rough, and possibly inaccurate, estimate. Complete inhibition at the site of action may be impossible to truly know. Thus, the absence of a therapeutic effect may indicate inaccurate estimates of target engagement at the site of action rather than true lack of an effect of the molecule. The definition of target saturation is unclear and should be better defined. Target saturation may not translate to efficacious dose.	Partly accepted. Text amended.

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		In this case, higher doses will not help to understand target mediated PD effects. However, evaluating higher doses (under close safety monitoring and if supported by the previous clinical and nonclinical data), will help understanding the off-target effects and potential safety issues to be encountered in later stages where PK variability (and potential target expression) may have significant variability. This is linked with previous comments regarding the critical relevance to evaluate higher doses in early clinical development to better predict safety risks and optimize risk management.	
426-428	47	**Comments:** It should be permissible to exceed the expected/anticipated therapeutic exposure in early trial to evaluate in a safe environment (phase 1 units) potential off target effects and exaggerated pharmacology which will happen in the real world when between patients variability is accounted for. **Proposed change:** “Target saturation should be taken into account, e.g. if the intended therapeutic effect is linked to enzyme inhibition, then the maximum dose should consider when complete inhibition is achieved and no further therapeutic effect is to be expected by increasing the dose. However, there might be a need in some circumstances (e.g. small molecule) to be able to exceed the expected/anticipated therapeutic exposure in early trials to evaluate in a safe environment (phase 1 units) potential off target effects and/or exaggeration of pharmacological effects already observed at therapeutic doses, which will emerge in the real world when between patients variability is accounted for. For trials or…”	Partly accepted. Text amended.
426-428	47	**Comments:** The true Exposure: Response relationship and connection between target engagement and efficacy is often unknown prior to human testing. High quality translatable biomarkers may not always be available to identify target efficacious clinical exposure. The target may be complete inhibition of the enzyme for efficacy then there are no exposure multiples i.e.	Partly accepted. Text amended.

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		supratherapeutic range for QT or DDI evaluations. **Proposed change:** Remove or recognize that there is sometimes a need to exceed Emax by several-fold (eg, high dose ≠ target saturation), as allowed by the safety data.	
426-428	47	**Comments:** The statement does not take into account the duration of effect. It implies, although does not state, that the complete inhibition would be at the end of the dose interval. In this scenario, no dose escalation would take place above the therapeutic dose and hence the tolerability of supratherapeutic doses will not be established in healthy volunteers (HVs)	Partly accepted. Text amended.
426-428	51	**Comments:** This section of the draft guideline does not take into account the duration of effect. It implies, although does not state, that the complete inhibition would be at the end of the dose interval. In this scenario, no dose escalation would take place above the therapeutic dose and hence the tolerability of supratherapeutic doses will not be established in healthy volunteers.	Partly accepted. Text amended.
426-428	51	**Comments:** Similar to our comments in lines above 424-425, BIO believes that further clarification is needed if FIH maximum single ascending dose (SAD) is a dose that causes complete inhibition. Moreover this statement is complicated by whether this is to be evaluated on a target occupancy biomarker or more functional biomarker, and the relationship of the functional biomarker with clinical efficacy. **Proposed change:** Target saturation should be taken into account, e.g. if the intended therapeutic effect is linked to enzyme inhibition, then the ~~maximum dose~~ anticipated therapeutic dose range (ATD) should consider when near complete occupancy and/or	Partly accepted. Text amended.

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		functional inhibition is achieved and little ~~no~~ further therapeutic effect is to be expected by increasing the dose (depending on the correlation between the functional endpoint and clinical efficacy).	
428	26	**Comments:** ACRO recommends rephrasing the text to more explicitly distinguish from an extended duration of therapeutic effect that may occur with an increased dose, possibly with the penalty of compromised safety or tolerability. **Proposed change:** Rephrase the text to read: "...and no increased therapeutic effect is to be expected…"	Partly accepted. Text amended.
428	47	**Comments:** This guideline currently considers primarily human cellular molecules as pharmacological target, but not pathogen specific molecules, for which susceptibility, strain variability as well as resistance development plays a major role when discussing the therapeutic or maximum dose. Therefore, we would propose to add information on this by adding one sentence in line 428. **Proposed change:** It is of note that variable susceptibility, strain variability as well as resistance development has to be considered for pathogen-targeting drugs (e.g. antibiotics, antivirals, antifungals).	Not accepted. Too specific detail.
429	17	**Comments:** The meaning of the text '(if applicable)' is unclear. **Proposed change:** Please clarify with an example.	Not accepted. Too specific detail.

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429	46	**Comments:** I think the first sentence should read: the highest achievable human exposure or the MTD documented in human subjects should be clearly.....	Not accepted. Too specific detail.
429-433	30	**Comments:** The issue that studies with MTD as the primary outcome should never be done in healthy volunteers is fundamentally important as such trials seem to be currently common. This paragraph should be at the top of this section and the patient vs healthy volunteer discussion re-ordered. The comment is given too little emphasis in its current position. **Proposed change:** Consider placing at the top of section 7.4 (currently line 406): A trial design using a maximum tolerated dose (MTD) as the primary objective is unethical for healthy volunteers. For trials or trial parts that include patients, using the MTD as an outcome may be considered but this should be clearly defined and not be exceeded once it has been determined. The potential therapeutic/clinically relevant dose (exposure) and the expected benefit/risk balance should always be considered when defining the dose range. Where patients are included in a study, consideration should be given to their co-morbidities which may alter the benefit/risk balance. It is important to distinguish between dose-limiting pharmacodynamic effects affecting tolerability e.g. mild undesired but not serious central effects from those with more serious implications for safety.	Not accepted. Too specific detail.
429-433	39	**Comments:** We agree on this proposal, but would have been happy to have here some orientation on MTD definition, especially for healthy volunteers. In addition we are not convinced to separate here and everywhere patient from healthy volunteers (with exception of anti-cancer drug)	Not accepted. Too specific detail.
429-	41	**Comments:**	Not accepted.

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433		Importantly, this section states that “A trial design using a MTD approach is considered to be unethical for healthy volunteers”. However, it should be further emphasised that escalation in order to determine the maximum tolerated dose should only be considered for patient studies where justified by the predicted and emerging PK and PD data and the potential benefit to the patient. This is currently implied, but should be stated more explicitly.	Too specific detail.
429-433	43	**Proposed change:** Add here the information on the dose limit in advanced cancer patients from section 7.7 (L. 464-467).	Not accepted. Too specific detail.
429-433	47	**Comments:** There are several published papers about MTD and they all point out to the critical definition of the criteria for MTD. MTD is to be defined by acceptable criteria. It should remain possible to study the MTD in healthy volunteer studies in certain conditions (see proposed text) **Proposed change:** For trials or trial parts that include patients, the maximum tolerated dose (MTD) (if applicable) should be clearly defined by acceptable criteria(without the need to give an absolute maximum value for either dose or exposure) and not be exceeded once it has been determined. The potential therapeutic/clinically relevant dose (exposure) and the expected benefit/risk balance should always be considered when defining the dose range For trials or trial parts that include healthy volunteers, the MTD may potentially be explored provided the anticipated human toxicities based on the relevant, preclinical toxicology studies are not severe and are monitorable and reversible.	Not accepted. Too specific detail.
429-433	51	**Comments:** There are several published papers about maximum tolerated dose (MTD) and they all discuss the critical definition of the criteria for MTD. MTD is to be defined by acceptable criteria. It is agreed that investigating the MTD in healthy subjects should no longer be an objective, although the maximum dose to be investigated in healthy subjects can be above the	Not accepted. Too specific detail.

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		efficacious dose range (see previous comment). **Proposed change:** For trials or trial parts that include patients, the maximum tolerated dose (MTD) (if applicable) should be clearly defined by acceptable criteria and not be exceeded once it has been determined.	
432	33	**Comments:** Designing a trial using a MTD approach as a primary objective can be considered as unethical in healthy volunteers. Nevertheless, reaching the MTD in healthy volunteers during a dose escalation is not unethical.	Partly accepted. Text amended.
432	40	**Comments:** Its states that 'A trial design using a MTD approach is considered to be unethical for healthy volunteers'. Is this meant to state that patients can be used in FIH / early CT trials when a MTD approach is unethical for healthy volunteers? As often in FIH we would determine the MTD in healthy volunteers, if deemed ethical. **Proposed change:** "A trial design using a MTP approach *without max dose predefined* is considered to be unethical."	Partly accepted. Text amended.
432-433	3	**Comments:** Welcome is the clear assertion (lines 432-433) that: "A trial design using a maximum tolerated dose approach is considered to be unethical for healthy volunteers".	Partly accepted. Text amended.
432-433	9	**Comments:** (last sentence): this sentence can be omitted because sometimes it can be very useful to know the MTD. Whether this is acceptable or not depends on the nature of the AEs.	Not accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
432-433	29	**Comments:** "A trial design using a MTD approach is considered to be unethical for healthy volunteers." This is the most important statement in the document and deserves amplification since it contrasts with the approach previously adopted by another regulator. It would be useful to explain what recent experience (eg the Bial trial in Rennes) has led to this conclusion. It would be unacceptable if this was subsequently watered down or ignored in practice. The approach is also surely unethical in non-therapeutic phase I trials in patient volunteers. In particular, some FTIM studies in patient volunteers aim to escalate doses until significant intolerability and/or toxicity appears although the patients have little significant prospect of benefit. If there are ethical and scientifically justifiable reasons for adopting this approach in a patient study then these should be carefully explained and contrasted with the data that could be expected to arise from alternative study designs using a more conservative dosing protocols.	Partly accepted. Text amended. Ethics consideration is outside the scope of the current document so changed to 'inappropriate'
432-433	51	**Proposed change:** A trial design using a MTD approach is ~~considered to be unethical~~ not recommended for healthy volunteers unless properly justified.	Partly accepted. Text amended.
432-433	53	**Comments:** The sentence "A trial design using a MTD approach is considered to be unethical for healthy volunteers" is too strict. The nature of the safety event considered to define the MTD is important to consider. If the safety event is non-life threatening (eg vomiting, itching,…), it should not be considered as unethical to define the MTD in healthy volunteers. In addition, for mild medical conditions, it should not be considered less ethical to conduct a phase 1 study in healthy volunteers compared to patients. Properly defining the MTD remains an important task to evaluate the benefit /risk and the safety margin of a new compound. **Proposed change:** The sentence should be deleted.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
434,	16	**Proposed change:** Would expand this section to guide investigators on the need for multiple MAD cohorts at non-therapeutic doses.	Not accepted. Too specific detail.
434,	22	**Comment and suggested change to chapter 7.5**: Suggest including that reliable data, including PK, from three consecutive single dose cohorts are sufficient to progress to multiple dose part of the study.	Not accepted. Too specific detail.
435-436	48	**Comments:** A minor edit to this sentence is required to reflect the sometimes staggered availability of PK analysis from dose cohorts. **Proposed change:** The selection of an appropriate dosing interval and duration of dosing for all multiple dosing cohorts and study parts should take into account the specific PK and PD characteristics of the IMP, the available non-clinical safety data, and **available** human PK, PD and safety data from subjects in previous single dose cohorts	Not accepted. Too specific detail.
435-439	29	**Comments:** “The selection of an appropriate dosing interval and duration of dosing for all multiple dosing cohorts and study parts should take into account the specific PK and PD characteristics of the IMP, the available non-clinical safety data, and human PK, PD and safety data from subjects in previous single dose cohorts. Particular attention should be paid to linear versus non-linear PK in the expected concentration range, the PK half-life versus duration of action and the potential for accumulation.” This helpful paragraph points to issues that would favour a more conservative design of the MAD phase that is currently widely adopted. It would be more helpful still if it addressed explicitly the question of when a “sentinel dosing” strategy analogous to that described above (L 575-8) for the SAD phase is appropriate in the MAD phase and when it may not be necessary.	Not accepted. Too specific detail.

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437	40	**Comments:** Is it clear enough here that doses should be studied as single dose prior to investigating them as repeat dose? As in repeat dosing should not consider doses that are greater than those studied in single dosing. For example, if 10 and 20mg have been studied under single dose, then 15mg can be studied under repeat dose, but 30mg repeat dose could not.	Not accepted. Too specific detail.
438-439	3	**Comments:** In moving from single to multiple dosing, the EMA Guidance correctly requires (lines 438-439) that: “particular attention should be paid to linear versus non-linear PK in the expected concentration range, the PK half-life versus duration of action and the potential for accumulation.”	General agreement.
439	46	**Proposed change:** Potential accumulation “for parent and/or metabolites”	Not accepted. Too specific detail.
441	20	**Comments:** The guidance states that the previous identified MTD should not be exceeded in the MAD without a substantial amendment. While this is generally true, there are some situations where the MTD following a single dose is predicted to be better tolerated by dose titration in a multiple dose setting (for example many CNS compounds are not well tolerated if a high single dose is given but titration over multiple doses leads to tolerability and therefore it may be appropriate to investigate higher doses in these circumstances). **Proposed change:** Suggest amending wording to clarify that in some circumstances the MTD identified in the SAD may be planned to be exceeded with appropriate scientific justification, appropriate safety monitoring and the use of dose titration.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
441-442	21	**Comment:** Reaching MTD should trigger stopping rules, therefore this sentence may be superfluous. **Proposed change:** To amend the text as follows: ~~However, previous MTD doses (and corresponding exposure and/or effects) should not be exceeded.~~ A maximum duration of dosing should be stated in the protocol for every cohort.	Partly accepted. Text amended.
441-443	30	**Comments:** These decisions should not be based around MTDs since there should be no ambition of reaching a MTD in a healthy volunteer study. Instead, previous highest doses should not be exceeded (and the emerging pharmacology should be considered) **Proposed change:** However, previous highest doses should not be exceeded (and the corresponding PK, PD and clinical effects should be carefully considered) unless tolerance occurs on repeated dosing (e.g. with opiates). A maximum duration of dosing should be stated in the protocol for every cohort.	Partly accepted. Text amended.
441-443	41	**Comments:** The statement here that a previous MTD should not be exceeded in later multiple dose cohorts is only applicable in instances where the MTD has been determined. As previously stated (lines 429-433), escalating the dose to determine the MTD should only be considered where this is justified. The guidance here should be extended to state that the highest dose previously administered in SAD cohorts should not be exceeded in MAD cohorts in instances where the MTD has not been determined.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
441-444	47	**Comments:** Depending on the nature of tolerability (and whether Cmax or AUC driven), if not a safety concern but a tolerability issue, the multiple dose portion of the study may evaluate dose titration design to overcome. When data supports at lower doses, the maximum dose in the multiple dose (following titration with or without accumulation) may exceed the exposure in the previous single dose part of the study. **Proposed change:** Suggest add language to guide dose titration design and allow higher doses or exposure in the multiple dose part than in the single dose part. Add wording that the choice AUC vs. Cmax may be justify depending on the nature of adverse effect.	Partly accepted. Text amended.
441-447	47	**Comments:** The guidance states that the previous identified MTD should not be exceeded in the MAD without a substantial amendment. However there are some situations where the MTD following a single dose is predicted to be better tolerated by dose titration in a multiple dose setting (for example many CNS compounds are not well tolerated if a high single dose is given but titration over multiple doses leads to tolerability and therefore it may be appropriate to investigate higher doses in these circumstances). **Proposed change:** “The chosen dose, as well as expected exposure after multiple dosing (Cmax and AUC0-t), should have been covered during preceding SAD parts/trials. If, however, emerging clinical data following multiple dosing suggests tolerance to adverse effects seen in a SAD part of a study whilst exposure remains below the predefined exposure threshold, a substantial amendment to the protocol to cover higher doses in a MAD part can be considered. Finally, in some circumstances the MTD identified in the SAD may be planned to be exceeded with appropriate scientific justification, appropriate safety monitoring and the use of dose titration “	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
442	20	**Comments:** The maximum duration of dosing should be set if appropriate to do so. There are exceptions to this – e.g. FIH in oncology patients who are benefitting from the treatment. There should be flexibility to continue to dose patients if appropriate.	Partly accepted. Text amended.
442-445	17	**Comments:** Use of the tem 'MTD' is misleading here. In lines 429–433, the guidance states that using a MTD approach is considered unethical in healthy volunteers. However, in line 442, the guidance states that previous MTD doses should not be exceeded in subjects receiving repeated doses. To avoid use of 'MTD' here, it would be clearer to state that, in moving from single-dose to repeated-dose studies, exposure should not exceed the highest exposure that has previously been shown to be safe and well tolerated in humans after a single dose. The guidance should also note that the first dose level to be administered in repeated doses should also incorporate a safety factor, to allow for possible accumulation. **Proposed change:** However, **dose levels** ~~previous MTD doses~~ (and corresponding exposure [C_{max} and AUC_{0-t}] and/or effects) **tested in repeated-dose trials** should not ~~be~~ exceed~~ed~~ **the highest dose level that has been shown to be safe and well tolerated in humans when administered as a single dose. The starting dose level in the first repeated-dose trial should also have a safety factor applied, to allow for possible accumulation,** and a maximum duration of dosing should be stated in the protocol for every ~~cohort~~**dose level**. ~~The chosen dose, as well as expected exposure after multiple dosing (C_{max} and AUC_{0-t}), should have been covered during preceding SAD parts/trials.~~	Partly accepted. Text amended.
443	47	**Comments:** It is stated that exposure in MD should be covered by SD exposure. If referring to all MD dose levels, one will have very limited possibilities to having overlapping SAD and MAD trials in phase 1 which will affect timelines. **Proposed change:** Should be specified to exposure in dosing interval, or exposure within a half-life interval. Because sooner or later MD	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		exposure will exceed SD exposure. Please clarify if "The chosen dose" refers only to the starting dose of the MAD trial, or if it refers to all chosen doses in the MAD trial.	
443-444	20	**Comments:** AUC_{0-t} would not be an appropriate measurement for multiple dose exposure and should be replaced with AUC at steady state over a dosing interval (AUC_{0-tau}). **Proposed change:** Please replace AUC_{0-t} with AUC_{0-tau}	Accepted. Text amended.
443-444	34	**Proposed change:** Please change AUC0-t to AUC0-tau	Accepted. Text amended.
444	22	**Comments:** PK parameters used are not appropriate. **Proposed change:** "The chosen dose, as well as expected exposure after multiple dosing ($C_{max,ss}$ and $AUC_{0-tau,ss}$), should have been covered during preceding SAD parts/trials (C_{max} and AUC_{0-t})."	Accepted. Text amended.
444	47	**Comments:** "...expected exposure after multiple dosing (Cmax and AUC0-t) should have been covered". AUC0-t is typically defined as AUC calculated to the last measured concentration **Proposed change:**	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Therefore AUC0-t would not be an appropriate measurement for multiple dose exposure and should be replaced with AUC at steady state over a dosing interval (AUCT).	
444	47	**Comments:** As a worst case, it appears important to refer to steady-state exposure, not just multiple dose PK **Proposed change:** The chosen dose, as well as expected steady-state exposure after multiple dosing (Cmax and AUC0-t), should have been covered during preceding SAD parts/trials expected exposure Please specify that AUC0-t is AUC0-tau, where tau is the dosing interval	Accepted. Text amended.
444	51	**Comments:** As a worst case, it appears important to refer to steady-state exposure, not just multiple dose PK. Additionally, BIO asks EMA to please specify that AUC0-t is AUC0-tau, where tau is the dosing interval. **Proposed change:** The chosen dose, as well as expected steady-state exposure after multiple dosing (Cmax and AUC0-tau), should have been covered during preceding SAD parts/trials.	Accepted. Text amended.
444-445	21	**Comments:** As long as the expected *exposure* after multiple dosing has been covered during preceding SAD parts/trials, it is not necessary that the chosen *dose* has also been covered. This would be overly prescriptive and may not be useful for many trials. **Proposed change:** To amend the text as follows:	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		"~~The chosen dose, as well as~~ The expected exposure after multiple dosing (C_{max} and AUC_{0-t}) should have been covered during preceding SAD parts/trials."	
445-446	47	**Comments:** It should be recommended that planned adaptations, subsequent to emerging clinical data evaluation, are pre-planned in the protocol (with clear criteria), so that substantial amendments are reserved for these situations that have not been foreseen or pre-planned.	Partly accepted. Text amended.
445-447	17	**Comments:** Tolerance can, in some cases, be reliably predicted based on class of IMP or pre-clinical data. It should be possible to pre-specify and justify in the protocol a dose escalation strategy, in anticipation of tolerance, in which higher dose levels may be tested in the MAD part than were tested in the SAD part. **Proposed change:** **If tolerance is likely, eg based on the class of IMP, a dose escalation strategy that allows higher dose levels in the MAD part than were tested in the SAD part may be pre-specified in the protocol.** If, however**, tolerance was not anticipated and** emerging clinical data following **repeated** dosing suggests tolerance to adverse effects seen in a SAD part of a study, a substantial amendment to the protocol to cover higher doses in a MAD part can be considered.	Partly accepted. Text amended.
445-447	21	**Comments:** The doses/dosing regimen for multiple dosing are usually not predefined in adaptive protocols and are set based on emerging SAD (and other available) data. Therefore this sentence should - for most IMPs - refer to exposure rather than dose. Furthermore - for some IMP - tolerance following multiple dosing (or up-titration) may be expected and the guidance should allow protocols to set rules for these scenarios. **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		To amend the text as follows: "If however, emerging data following multiple dosing suggest tolerance to **specific** adverse effects **seen at similar exposure levels in** a SAD **(or another)** part a study, a substantial amendment to the protocol to cover **the use of these exposure levels** in a MAD part can be considered. **If tolerance after multiple dosing (or up-titration) is expected at the time of protocol writing, this should be taken into account when setting the rules for moving from single to multiple dosing.**"	
445-447	46	**Comments:** A substantial amendment is not the objective, just the mean to achieve a change, **Proposed change:** "If, however, ermerging clinical data...suggests tolerance..., higher doses in a MAD might be considered and would necessitate a substantial amendment." In addition, guidance usually not specific on the mean, so suggest replacing by: "and would need to be communicated to the CA and ECs, as applicable". (in line with wording in line 509)	Partly accepted. Text amended.
445-447	51	**Comments:** This scenario should be accounted for in the protocol via flexible wording to enable dose adjustment without having to go through a substantial amendment. **Proposed change:** The chosen dose, as well as expected exposure after multiple dosing (Cmax and AUC0-tau), should have been covered during preceding SAD parts/trials. If, however, emerging clinical data following multiple dosing suggests tolerance to adverse effects seen in a SAD part of a study whilst exposure remains below the predefined exposure threshold, ~~a substantial amendment to the protocol to cover~~ higher doses in a MAD part can be considered (this scenario should have been described and approved in the protocol).	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
446	30	**Comments:** This situation is something that should generally be considered in advance and covered in the protocol. A substantial amendment should not be required.	Partly accepted. Text amended.
449	10	**Comments:** The IMP administration should be characterised and justified not only by route but also by rate. **Proposed change:** The choice of route and rate of IMP administration for dosing in humans should be justified based on the non-clinical data.	Not accepted. Too specific detail.
449-450	47	**Proposed change:** "The choice of route of administration for dosing in humans should be justified based on the non-clinical data, ***and the intended therapeutic use***."	Partly accepted. Text amended.
451	5	**Comments:** The difference between slow infusion and slow bolus is not completely clear. **Proposed change:** When the administration route is intravenous administration, a slow infusion is preferred over a fast infusion.	Partly accepted. Text amended.
451	17	**Comments:** 'Slow' bolus is an ill-defined term. **Proposed change:** Delete 'slow'.	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
451	30	**Comments:** This statement should be made stronger. **Proposed change:** Intravenous infusions should generally be administered slowly. While the duration of infusion will depend to some extent on PK, typical infusion times vary from 1 to 4 hours but may need to be longer. It is rarely justified to administer an IMP as a bolus in early studies, even if such a regimen is ultimately intended in clinical practice.	Partly accepted. Text amended.
451	47	**Comments:** Slow infusion vs slow bolus could be more clearly defined. In addition, it is part of normal clinical practice routines and compound dependent, which makes it difficult to motivate as part of the guideline. **Proposed change:** Delete sentence.	Partly accepted. Text amended.
451-452	13	**Comments:** Please consider to add an example to clarify why a slow infusion may be more appropriate than a slow bolus. **Proposed change:** Please consider to add "*Especially in the case of monoclonal antibodies which may cause infusion-related reactions*."	Not accepted. Too specific detail.
451-452	21	**Comments:** The statement that a slow infusion may be more appropriate than a slow bolus refers to one specific mode of administration, and it is unclear why this (common-sense) statement -out of many other potential modes of administration for different IMPs - has been selected for the guideline.	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: We propose deleting the statement or alternatively adding other relevant examples.	
451-452	29	**Comments:** What is the distinction between a “slow infusion” and a “slow bolus”? It is assumed the intention here is to encourage the use of a mechanical infusion pump to facilitate accurate and consistent drug delivery in which case the proposed change would be: **Proposed change:** “In the case of an intravenous administration, a slow infusion **using a mechanical infusion pump** may be more appropriate than a slow bolus **delivered manually by slow injection.**	Not accepted. Too specific detail.
451-452	51	**Comments:** BIO suggests including examples of the durations for slow infusion and slow bolus as these would be helpful to sponsors.	Not accepted. Too specific detail.
453	47	**Comments:** Section 7.7. Patients: It would be helpful to provide guidance for studies in patients where the drug is administered by the intravitreal or similar routes. In such circumstances, it is not readily possible to relate systemic exposure to drug with toxicities at the site of administration, often due to the low systemic exposure to drug. The same challenge will apply to studies in HVs where the drug is administered by the ocular topical, dermal, inhalation route	Not accepted. Too specific detail.
453	47	**Comments:** It has not been clear if all text up until now was HV only,	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: This title should perhaps be something like "special considerations for involving patients"	
453 454-461 464-467	43	**Comments:** In some instances, the guideline provides information on studies in patients separated out to a specific section while in other cases it is included together with the HV information. **Proposed change:** Move the information in L. 454-461/L. 464-467 to section 7.2 Starting dose and section 7.4 Maximum dose and dose range, respectively.	Partly accepted. Text amended.
453-469	51	**Comments:** BIO believes it would be helpful to provide guidance for studies in patients where the drug is administered by the intravitreal or similar routes. In such circumstances, it is not readily possible to relate systemic exposure to drug with toxicities at the site of administration, often due to the low systemic exposure to drug. The same challenge will apply to studies in healthy volunteers where the drug is administered by the ocular topical, dermal, inhalation route.	Not accepted. Too specific detail.
454	47	**Comments:** Similar considerations for starting dose as outlined in section 7.2 apply It is also referred to the ICH S9 document further down in the document. With regards to starting dose in section 7.2 and ICH S9 in oncology patients – ICH S9 guidance states that " the goal of selecting the start dose is to administer a pharmacologically active dose that is reasonably safe to use" – it is not to identify a dose that is expected to have a minimal pharmacological effect and is reasonably safe to use. These different	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		considerations for healthy volunteers and oncology patients should be highlighted.	
454-457	48	**Comments:** Similarly to our previous comment related to use of doses in healthy subjects below that which would elicit a PD response, we suggest the use of doses in patients which elicit a minimal PD effect is equally unjustified.	Partly accepted. Text amended.
454-463	37	**Comments:** This section is a welcome addition to the guidelines, and reflects a trend over the last 10 years to evaluate safety/PK/PD in patients as early as possible in the drug development process. The same comments as for section 7.2 are also applicable [comments on section 7.2: We agree that all available *in vitro* and *in vivo* data should be taken into account to determine not only MABEL, but PAD and ATD. We also suggest that any additional non-clinical information that can help guide PK-PD modelling (e.g. interaction with transporters, Cytochrome P450 enzymes, Biopharmaceutics Drug Disposition Classification etc) should be considered where possible.]	Partly accepted. Text amended.
456-457	30	**Comments:** How does one define 'reasonably safe to use'? Better to remove the word 'reasonably'. **Proposed change:** is to identify a dose that is expected to have a minimal pharmacological effect and is safe to use	Accepted. Text amended.
458-459	47	**Comments:** For the discussion of FiH studies to be conducted in part or in full in patients, it would be helpful to distinguish between cohorts enrolling patients with administration of IMP with and without therapeutic intent, i.e. with the prospect of possible therapeutic benefit such as in Oncology / hematology patients. **Proposed change:**	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		"In ~~**some**~~ instances **where the IMP is administered to patients with therapeutic intent**, a starting dose that is substantially lower than the human expected therapeutic dose may not be appropriate".	
458-461	47	**Comments:** It is not clear what is meant by the sentence "In some instances, a starting dose that is substantially lower than the human expected therapeutic dose may not be appropriate. If a higher dose is proposed, a rationale should be provided and the subjects included in the CT should be informed". Does this mean a dose higher than the expected therapeutic dose in humans can be used as a starting dose? And in such cases the subjects have to be informed about this fact?	Not accepted. Reference is to higher than 'substantially lower'.
459	46	**Comments:** I assume the statement "In some instances..." applies to early CTs not FIH (on the contrary, the issue would be to start with doses not low enough).	Not accepted. Too specific detail.
459-460	26	**Comments:** It is not clear whether the statement "If a higher dose is proposed…." refers to the human expected therapeutic dose (which is higher than the typically very low starting dose used in FIH studies) or to a dose that is higher than the human expected therapeutic dose, and ACRO recommends that this is clarified. **Proposed change:** Make clear what the phrase "If a higher dose is proposed…." refers to.	Accepted. Sentence deleted.
460	46	**Comments:** To clarify what "higher dose" refers to, i assume higher dose "than the human expected therapeutic dose"?	Accepted. Sentence deleted.
461	9	**Comments:**	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Documentation on information required? Eg in ICF or on source documentation?	detail.
462	9	**Comments:** Is a single dose design needed/ethical in patients (risk/benefit)? At this moment most combined protocols have SAD in HNV's and MAD in patients.	Partly accepted. Text amended.
462, 464	40	**Comments:** It mentions the case of moving from healthy volunteers to patients; and that there are other approaches that could be used in specific situations. But it may be worthwhile mentioning that the FIH studies could be studied only in patients (eg oncology), and that is some situations healthy volunteers would not be investigated.	Partly accepted. Text amended.
462-463	10	**Comments:** The reason for this requirement is unclear and is not common and established practice. If the PK of an IMP is considered to be substantially different in patients compared to healthy subjects, then the data from healthy subjects are not predictive and all clinical trial should be performed in patients only. If the PK is expected to be similar in patients, then multiple dose administration may be done right away. **Proposed change:** Lines 462 and 463 should be deleted.	Partly accepted. Text amended.
462-463	16	**Comments:** If MAD in healthy volunteers is available, should the rec of SAD in patients be to start at the therapeutic dose from the MAD in healthy volunteers?	Partly accepted. Text amended.
462-463	20	**Comments:** The IQ appreciates the Agency's openness on the potential inclusion of limited patient cohorts as part of an integrated FIH	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		study. However, initiation of dosing in patients with single doses after demonstration of safety following repeat dosing in healthy volunteers may be overly conservative and could lead to unnecessarily prolonged studies. It is appropriate in most cases to initiate multiple doses in patients following demonstration of safety and tolerability at a comparable or higher dose level in healthy volunteers, although, it is appreciated in some cases the more conservative approach may be appropriate. **Proposed change:** In some circumstances, when moving from healthy volunteers to exploratory patient studies, consideration may be given to reverting to a single dose design (with dose escalation as appropriate) in the first patient cohort.	
462-463	21	**Comments:** The statement that a single (escalating) dose design in patients should be considered when moving from healthy volunteers to patients appears very prescriptive. A single dose design in patients may be appropriate in certain circumstances, but would rarely follow a multiple dose design in healthy volunteers. Single dose in patients following heathy volunteers should not be a routine consideration and its absence should not require justification in a CT protocol. **Proposed change:** We propose deleting the statement.	Partly accepted. Text amended.
462-463	23	**Comments:** Reverting to a single dose assessment in patients after first having tested single and multiple ascending doses in healthy volunteers would only be informative and meaningful in case large exposure differences may be expected between healthy volunteers and patients. Therefore, this consideration should only occur in cases where SAD assessment in patients is meaningful. For example a drug that is metabolized in the liver in patients with hepatic disease. **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		"When moving from healthy volunteers to patients, consideration should be given to reverting to a single dose design (with dose escalation as appropriate) in the first patient cohort**, in case large exposure differences are expected between healthy volunteers and patients**."	
462-463	27	**Comments:** Additional clarity is required to define the circumstances under which it would be necessary appropriate to conduct an additional Single Ascending Dose study in patients. **Proposed change:** When moving from healthy volunteers to patients, consideration should be given to reverting to a single dose design (with dose escalation as appropriate) in the first patient cohort in order to explore higher exposures in this population if MTD was not reached in the HV study, the risk/benefit profile is acceptable, and based on exposure/response modelling a higher exposure is anticipated to provide additional clinical benefit.	Partly accepted. Text amended.
462-463	30	**Comments:** It should rarely be necessary to revert to a single dose design for patients when the safety of multiple doses has been established in healthy volunteers. Use of sentinel (lead subjects) with a defined interval between patients may be justified. **Proposed change:** When moving from healthy volunteers to patients, it is rarely necessary to revert to a SAD design for patients when the safety of multiple doses has been established in healthy volunteers. Use of sentinel (lead subjects) with a defined interval between patients and careful review of PK, PD and safety data may be justified with.	Partly accepted. Text amended.
462-463	33	**Comments:** The reason for this requirement is unclear and is not common and established practice. If the PK is expected to be similar	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		in patients, then multiple dose administration may be done right away. SAD in healthy volunteers then MAD in patients is a common design. **Proposed change:** Lines 462 and 463 should be deleted.	
462-463	34	**Comments:** Please clarify reverting to a single dose design (with dose escalations as appropriate) in the first patient cohort.	Partly accepted. Text amended.
462-463	39	**Comments:** Moving from Heathy to Patients, single dose might be skipped or simplified versus the design used in healthy volunteers	Partly accepted. Text amended.
462-463	47	**Comments:** This sentence is excessively vague. It's not clear in which situations it would be advisable or even beneficial to revert to single dose escalation for patients. The statement should be removed or changed to clarify the circumstances in which it would be an unacceptable risk to proceed from a MAD in healthy volunteers to a MAD in patients. These lines imply that patients are likely to be more sensitive to a compound than healthy subjects. This is frequently untrue depending on the therapeutic area, e.g., antipsychotics. **2 alternative proposed changes:** Delete the text: ~~1) "When moving from healthy volunteers to patients, consideration should be given to reverting to a single dose design (with dose escalation as appropriate) in the first patient cohort."~~ OR	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		"When moving from healthy volunteers to patients, consideration should be given to reverting to a single dose design (with dose escalation as appropriate) in the first patient cohort***, when the available data suggest that the patient population may be more susceptible to on- or off-target toxicity compared to healthy volunteers***."	
462-463	51	**Comments:** BIO believes this approach is very conservative and would not be necessary in some situations. As such, we propose that it is limited to specific situations. Additionally, we note that if supratherapeutic doses cannot be administered to healthy volunteers, then subtherapeutic doses will have to be evaluated in studies in patients. Administering single doses to patients may make clinical trial recruitment challenging since the patients will derive no therapeutic benefit from the administration of a single dose. **Proposed change:** In some particular circumstances (i.e., major difference expected in exposure between patients and healthy volunteers, or for molecules with a narrow therapeutic index) when moving from healthy volunteers to patients, consideration should be given to reverting to a single dose design (with dose escalation as appropriate) in the first patient cohort.	Partly accepted. Text amended.
464-465	47	"Other approaches may also be considered in specific situations, e.g. for studies with conventional cytotoxic IMPs in oncology patients (see ICH S9)." **Comments:** Suggest deletion of "cytoxic" because this would also apply to non-cytoxic IMPs in oncology patients. This can also apply to other disease areas in which patients have an equally significant prognosis and/or rapid deterioration and therefore have an increased tolerance for risk in the study, e.g. in certain neurological diseases. **Proposed change:** **Other approaches may also be considered in specific situations, e.g. for studies enrolling patients with devastating diseases that impact mortality or cause significant deterioration in quality of life, e.g.**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		conventional cytotoxic IMPs in oncology patients (see ICH S9) or in patients with certain neurological diseases.	
464-467	47	**Comments:** The guidance states that in oncology trials dose escalation is not limited by the highest dose or exposure tested in the non-clinical studies. However there is no clarity on the situation in healthy volunteers and whether dosing above the levels tested in non-clinical studies (or the NOAEL) can be performed or not. If possible it would be preferable to replace the term “specific situations” with “certain situations” in order to avoid confusion with the GVP term “special situations” defined in Module VI of the guideline on GVP.	Partly accepted. Text amended.
464-469	13	**Comments:** The part on oncology patients and the paediatric population are two examples of a special population/situation. We suggest to start with a general sentence followed by these two (or more) examples **Proposed change:** Please consider to start with the general sentence: “*Some special population/situations may deserve additional specific consideration*.” Thereafter the oncology patients, paediatric population and more examples (e.g. elderly) can be discussed.	Partly accepted. Text amended.
465-467	20	**Proposed change:** “In general, the highest dose or exposure tested in the non-clinical studies may not limit the dose-escalation or highest dose investigated in a CT in patients with advanced cancer and also in other devastating diseases if appropriately justified.	Partly accepted. Text amended.
465-	34	**Proposed change (if any)**	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
467		Please consider "In general, the highest dose or exposure tested in the non-clinical studies may not limit the dose-escalation or highest dose investigated in a CT in patients with advanced cancer and other life limiting and devastating diseases, if appropriately justified."	detail.
465-467	47	**Comments:** It is unclear whether or not this is limited to S9 type indications. If there are absolutely no clinical safety signals and provided subject monitoring is robust, should there be a dose cap based on the highest dose tested non-clinically? Dose escalation beyond the highest non-clinical exposures ought not be limited to "life-limiting" disease; "life-limiting" is an ambiguous term. **Proposed change:** "In general, the highest dose or exposure tested in the non-clinical studies may not limit the dose-escalation or highest dose investigated in a CT in patients with advanced cancer and also in other ~~life-limiting diseases~~ ***diseases that would impact mortality or would cause significant deterioration in quality of life*** if appropriately justified."	Not accepted. Too specific detail.
468-469	20	**Proposed change:** "Furthermore, some special populations, such as pediatric populations or patients with rare diseases, may deserve additional specific considerations (as per ICH E11)."	Not accepted. Too specific detail.
468-469	30	**Comments:** It should be made clearer which other patient groups could be regarded as special populations. **Proposed change:** Furthermore, some special populations, such as populations at the extremes of age (paediatrics, elderly), renal impairment populations and hepatic impairment populations, may deserve additional specific considerations.	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
468-469	34	**Proposed change:** Please consider “Furthermore, some special populations, such as the paediatric or rare disease population, may deserve additional specific considerations (as per ICH E11).”	Not accepted. Too specific detail.
470	13	**Comments:** In the non-clinical part a new sentence is included “The quality of documents supporting the CT application should be state -of -the -art in format (e.g. as per Good Clinical Practice (GCP))”, which is considered relevant for section 8 as well. **Proposed change:** We propose to include a sentence referring to GCP in the beginning of the clinical section 8.	Partly accepted. Text amended.
471-487	26	**Comments:** ACRO recommends that formulation (e.g., osmolality and titratable acidity), volume and speed of administration, fed / fasted, be added to the list of bullet points. ACRO also recommends adding a sentence to this section to confirm the importance of adding safety biomarkers that specifically monitor any observed toxicity as a risk mitigation measure. **Proposed change:** Add formulation, volume and speed of administration, and fed / fasted to the list of bullet points, and add a sentence to confirm the importance of adding safety biomarkers that specifically monitor any observed toxicity as a risk mitigation measure.	Partly accepted. Text amended.
471-490	40	**Comments:** I would expect this section to include the incorporation of sentinel subjects as an aspect for consideration (although I note this is covered in 8.2.6).	Not accepted. Too specific detail.
471-	42	**Comments:**	Not accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
490		It is recommended that EMA consider not only listing risk factors but also discussing risk mitigation strategies for the risk factors. In addition, add information regarding the EMA current thinking of the application of QRM and use of quality tolerance limits in FIH studies; notably for integrated protocols as noted in ICH E6 R2	Too specific detail.
474	46	**Comments:** Safety should not be compromised…in the interest of speed", the time perspective is included in the sentence before + this sentence gives the impression this could have been an option chosen on purpose in the past or could still be chosen by some, I would delete.	Not accepted.
474-475	3	**Comments:** In Section 8 on planning and conduct of FIH and early clinical trials, the EMA Guidance highlights the time available for integrated assessment and clearly states (lines 474-475) that: "Safety should not be compromised in the interest of speed of acquiring data or for logistical reasons".	General agreement.
479	17	**Comments:** Maximum dose in first-in-human studies is almost always expressed as a maximum exposure. **Proposed change:** first/starting dose, maximum dose **and/or exposure** and ~~maximal~~ **maximum** duration of the treatment;	Partly accepted. Text amended.
480-481	16	**Proposed change:** Add safety parameters necessary to monitor and intensity of monitoring?	Accepted. Text amended.
481	5	**Comments:** It is unclear what is meant with "the half-life (PK/PD) of the IMP if the same subjects are participating in multiple cohorts."	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
481	10	**Comments:** The half-life of a compound is not an aspect of a trial that can be designed. If the wash-out time was meant, the wording should be adapted as follows. **Proposed change:** “wash-out time for the same subjects participating in multiple IMP administration periods considering the half-life of the IMP”	Partly accepted. Text amended.
481	13	**Comments:** The text “*A crossover design with an appropriate washout period may be incorporated, for example to evaluate food effect in the fed and fasted states. Normally a washout for at least 5 elimination half-lives is necessary. PD effects can last longer than the systemic exposure and even more than 5 PK half-lives and in these cases the wash-out period should be expressed effectively in PD duration.”* Is removed completely from this section. The remark on half live is included in the bullet points in the general aspect section, however, the information on number of half-lives necessary is know missing. **Proposed change:** We propose to include this in the bullet-point (in section 8.1).	Not accepted. Too specific detail.
481	24	**Comments:** Are we sure that multiple participations of the same subjects to different cohorts is justifyable?	Yes.
483	9	**Comments:** Guidelines on staggered/sentinel dosing	General agreement.
483,	31	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
574		Special considerations should be added for FIH international multicentre trials. The sponsor must ensure that the interval between dosing of subjects in such a setting is respected if the cohort is open in different sites (especially in multicentre trials with different time zones).	Text amended. Different sites referenced in the guideline.
486	21	**Comments:** Stopping rules deal with situations in which a number of significant (and usually severe and/or serious) toxicities lead to stopping (part of) a trial. Stopping rules are therefore a subset of rules for dealing with toxicities caused by IMPs. We therefore suggest amending the term to "toxicity/stopping rules". **Proposed change:** To amend the term "stopping rules" to **"toxicity/stopping rules"**.	Not accepted. Stopping rules do not only relate to toxicity.
487	16	**Proposed change:** Add interim PK analyses as a risk mitigation activity.	Not accepted. Too specific detail.
488	16	**Proposed change:** Address the appropriate numbers of placebos per cohort Can more guidance be provided as to when a sentinel subject is needed?	Not accepted. Too specific detail.
488	17	**Comments:** Most first-in-human/early clinical trials include placebo **Proposed change:** It is recognised that placebo is ~~often~~ **almost always** included as part of the design of FIH/early CTs.	The use of placebo was frequently discussed throughout the

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			guideline.
488	32	**Comments:** Please remove this sentence as it does not provide guidance. **Proposed change:** ~~It is recognised that placebo is often included as part of the design of FIH/early CTs.~~	Not accepted. Too specific detail.
489	5	**Comments:** Good initiative. PD measure should be included unless not available, with an explanation why no PD marker is available.	General agreement.
489	6	**Comments:** The precise location for the recommended of the inclusion of a PD measure, when appropriate or feasible, should be stated. **Proposed change:** Suggest to clearly state that this information is to be included in the protocol, and perhaps also reiterated in the IB in the section 'Guidance for the Investigator'.	Not accepted. Too specific detail.
489	34	**Comments:** Please be more specific as "appropriate and feasible" may have many interpretations and place a heavy burden on identifying a dose responsive PD marker. For rare diseases, it can be very challenging to identify a true dose responsive marker given the small population. Also, when the mode of action is replacement of a missing enzyme (ERT), the PD marker may not be evaluable once steady state occurs during multi dosing.	Not accepted. Too specific detail.
489 &	20	**Comments:**	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
490		Robust validated/qualified assays to investigate PD may not be typically available at time of early studies; thus, the text should be considered to more align with current drug development. **Proposed change:** It is understood that PD measures may not have been sufficiently developed during early clinical trials. Thus, a PD measure may be included, when appropriate and feasible, in order to facilitate the link with the non-clinical experience and potentially support between dose PD assessments to aid dose escalation decisions.	detail.
489 & 490	47	**Comments:** Robust validated/qualified assays to investigate PD may not be typically available at time of early, thus, it text should be considered to more align with current drug development. **Proposed change:** It is understood that PD measures may not have been sufficiently developed during early clinical trials. Thus, a PD measure may be included, when appropriate and feasible, in order to facilitate the link with the non-clinical experience and potentially support between dose PD assessments to aid dose escalation decisions.	Not accepted. Too specific detail.
489-490	29	**Comments:** “It is recommended that a PD measure is included, when appropriate and feasible, in order to facilitate the link with the non-clinical experience and support dose escalation decisions.” This is helpful but may discourage some sponsors from including PD measurements, to avoid delay in awaiting PD data for dose escalation decisions since measures of PD may require special handling and best be batched for assay. It might be helpful to require the protocol to spell out where PD data are required for dose escalation and to require a justification when this is not the case?	Not accepted. Too specific detail.
489-490	47	**Comments:** Of note, the term, “biomarker”, does not feature even once in the current version of the draft CHMP Guidance. This is	Not accepted. Too specific detail here.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		remarkable especially since the FiH study will provide the first opportunity to implement the proposed biomarker strategy of the molecule concerned in man. In particular, reference should be made to translational biomarkers to support target engagement. **Proposed change:** "It is recommended that a PD measure **or biomarker** ~~**is**~~**be** included~~**, when appropriate and feasible,**~~ in order to ~~**facilitate**~~**establish** the link with non-clinical ~~**experience**~~**data**, support **proof of target engagement, and inform** dose escalation decisions".	Term 'biomarker' now in section 4.
493-496	41	**Comments:** The protocol should also identify the minimum data that will be considered for decisions relating to progressing the trial, including decisions to proceed to the next part where an integrated protocol is in use.	Not accepted. Too specific detail.
495	32	**Comments:** The word "documented" should added to the text, as it is considered important that the decision to proceed to the next study part should be documented. **Proposed change:** If there is an integrated protocol there should be a documented decision at a predefined time point on proceeding to the next part.	Not accepted. Too specific detail.
495-496	30	**Comments:** More information on the decision-making process would be helpful **Proposed change:** If there is an integrated protocol, there should be a decision at a predefined time point on proceeding to the next part.	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		The data required for a decision to escalate should be described, as well as the people who will take this decision.	
497-499	3	**Comments:** The EMA Guidance could usefully make graphical representation a requirement, not just an encouragement, as in: "Graphical representation of the overall scheme of the proposed trial in real-time, showing intervals to allow rolling review, timing of all reviews and decision points as well as any overlap between phases or parts, is encouraged" (lines 497-499).	Not accepted. Too specific detail.
497-499	43	**Comments:** Further clarification as to what is meant by the "graphical representation of the overall scheme of the proposed trial in real-time showing intervals to allow rolling review" would be welcome. In instances where highly flexible designs are needed, such as for oncology FIH studies, it should stay optional.	Not accepted. Too specific detail.
499	26	**Comments:** In order to explain the advantages of a graphical approach, ACRO recommends the following text, in place of the phrase "is encouraged". **Proposed change:** Replace "is encouraged" with "is helpful to users and competent authority/ethics committee reviewers".	Not accepted. Too specific detail.
500-501	16	**Comments:** Any recommendations on how to justify the N for each cohort and the proportion of drug:placebo within a cohort?	Not accepted. Too specific detail.
500-501	42	**Comments:** The reference to 'active treatment' does not distinguish between an investigational and active comparator treatment.	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Details on the size of the cohorts, including how many subjects receive the investigational product, are on ~~active~~ comparator and how many are on placebo treatment should be included and justified.	
500-501	50	**Comments:** Justification of sample size (on active drug and/or placebo) cannot be done on a statistical basis in small sample size cohorts typical of early/FIH trials. Please provide an example of an acceptable sample size range for a cohort in a FIH SAD/MAD trial; e.g., 6 on active, 2 on placebo in each escalation cohort.	Not accepted. Too specific detail.
502	16	**Comments:** For integrated protocols: can subjects participate in more than 1 part? Can screening laboratory tests be used for more than 1 part?	Not accepted. Too specific detail.
502	30	**Comments:** Please define what is meant by integrated protocols, since they can have several forms.	Not accepted. Too specific detail.
502	53	**Comments:** We suggest this section details the part related to the cohorts addition when the MTD is reached and clinical oncology indications are explored	Not accepted. Too specific detail.
503-520	37	**Comments:** The clarification of considerations for integrated protocols is welcomed. We suggest that PK modelling should be explicitly suggested as a requirement (where applicable) as part of the data required when moving from SAD to MAD parts.	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
506-509	47	**Comment:** In rare instances, decisions with respect to the conduct of distinct components of a FiH study with integrated protocol can be informed by preclinical data that will become available after initiation of the study (e.g. additional tox data with longer duration of exposure). The original FiH study protocol may be written such that changes in the conduct informed by additional preclinical data does not require a substantial amendment. As such, there is no strict requirement for all preclinical data to be available prior to initiation of the study. **Proposed change:** Within an integrated protocol all parts need to be predefined, including possible modifications, with specification of existing **or forthcoming** data and information, e.g. ~~**all**~~ non-clinical and, if available, clinical data".	Partly accepted. Text amended.
508	22	**Comments:** What is meant by "communicated" in this context? An amendment? Please clarify. **Proposed change:** "Any changes outside the predefined criteria should be ~~communicated~~ *implemented in a substantial amendment for approval by* ~~to~~ the competent authority(ies) and ethics committee(s), as applicable."	Partly accepted. Text amended.
508-509	13	**Comments:** In section 7 (dosing) the term *substantial amendment* is used several times, while in this section *to the competent authority(ies) and ethics committee(s), as applicable*" is used. **Proposed change:** We propose to use OR "*substantional amendment*" OR "*to the competent authority(ies) and ethics committee(s), as applicable*", in a consistent manner.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
511	24	**Comments:** conditions permitting overlap between SAD and MAD administrations must be specified in this guideline	Partly accepted. Text amended.
511	30	**Comments:** The overlap should not include higher MAD doses than already studied in the SAD part. This is made explicit in the subsequent two paragraphs (lines 514 and 518), and could usefully be added here. **Proposed change:** A certain overlap of SAD and MAD parts may be considered acceptable, provided the dose chosen is equal to or lower than that which was reached in a concluded preceding SAD cohort where all relevant data has been reviewed and no dose escalation stopping criteria were met.	Partly accepted. Text amended. Cross-reference added.
511-513	5	**Comments:** You should be careful that people will measure less data in the SAD to be able to start the MAD part as soon as possible. Also you can only justify this only after the data is known. **Proposed change:** Use "All available relevant data".	Not accepted. Too specific detail.
511-513	16	**Comments:** More details and clarity on this? e.g. how many cohorts in the SAD before starting the MAD part? Need for PK data analysis before starting the MAD?	Not accepted. Too specific detail.
511-513	47	**Comments:** These sections make a distinction between SAD and MAD phases of clinical development. We propose the guideline allows for some flexibility based on scientific justification to allow blurring of these lines, when appropriate. An additional	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		paragraph to discuss the possibility of SAD and MAD overlap is suggested for Section 7.5. **Proposed change:** Line 511-513: ~~A certain~~ **O**~~o~~verlap of SAD and MAD parts may be considered acceptable. However, any overlap should be scientifically justified and supported by a decision-tree and a review of the available data before deciding on starting the MAD part.	
512	26	**Comments:** ACRO recommends expanding the statement “supported by a decision-tree” as proposed below. **Proposed change:** Amend the statement to read “supported by a pre-defined decision-tree”.	Partly accepted. Text amended.
512	47	**Comments:** Decision tree technique potentially not generally implementable. **Proposed change:** Replace "decision-tree" with "composite set of data forming the decision"	Partly accepted. Text amended.
513	10	**Comments:** For this paragraph, a reference should be made to section 7.5. **Proposed change:** Add a reference to section 7.5.	Accepted. Text amended. Cross reference added.
514	26	**Comments:**	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		ACRO recommends that, in case exposure is expected to be significantly higher after administration with food (e.g., an IMP with low aqueous solubility and (very) low bioavailability in animals), an additional safety factor should be considered. The experience of ACRO members is that the effect of food on exposure can be up to 30-fold. **Proposed change:** Add a statement to require that an additional safety factor is used in cases where exposure is expected to be significantly higher after administration with food.	detail.
514	47	**Comments:** Lack of mentioning combination with already approved drug/drug-drug interaction studies. This is particular important if the IMP combine pharmacological principles to improve tolerability by allowing lower doses or improve PD or strive for additive effect by combining with well-known compounds. **Proposed change:** Suggest adding DD interaction with approved drug in the bracket: (e.g. food interaction (FI), or drug-drug (DD) interaction with already approved drug).	Not accepted. Too specific detail.
517	46	**Comments:** For food effect cohort and if a clinically significant increase in exposure is expected with food (sometimes up to 5-fold or less commonly 10-fold), this general rule is misleading	Not accepted. Too specific detail.
518	10	**Comments:** Food interaction (FI) trials are usually conducted with single dose administration. **Proposed change:** Delete “FI”	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
518-519	22	**Comments:** This sentence is ambiguous. How is “earlier” defined? Such a restriction is not considered of use if adequate exposure data is available. **Proposed change:** Consider to change wording.	Not accepted. Too specific detail.
518-520	20	**Comments:** The IQ welcomes the Agency’s flexibility regarding integrated protocols. However, a restriction on initiating study parts in parallel is unnecessarily conservative. **Proposed change:** “Other study parts that involve multiple dosing (e.g. FI and drug-drug interaction) should not overlap with any earlier could be conducted in parallel with the SAD or MAD cohorts., provided the dose and duration chosen and the expected exposures are lower than those attained in a previously concluded cohort”.	Partly accepted. Text amended.
518-520	21	**Comments:** One of the main benefits of using adaptive integrated protocols is the ability to overlap study parts as soon as the relevant data from other parts of the trial have been reviewed to allow for progression to a new study part. This has a significant time-saving effect and allows entire early phase trial programmes to be run in less than one year. It is beneficial, justified and safe to overlap food interaction or drug-drug-interaction parts with earlier SAD or MAD parts of a trial as long as the relevant data (PK, safety and tolerability, PD where applicable) allows. The protocol needs to contain a definition of what is “relevant” data (e.g. exposures that cover a potential food effect or drug-drug-interaction). **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		To amend the text as follows: Other study parts that involve multiple dosing (e.g. FI and drug-interaction) **can overlap with earlier SAD and MAD cohorts as long as the CT protocol clearly defines the relevant data that should be reviewed before starting these parts.** ~~Deviation from this should always be clearly defined in the protocol.~~	
518-520	29	**Comments:** "Other study parts that involve multiple dosing (e.g. FI and drug-drug interaction) should not overlap with any earlier SAD or MAD cohorts. All relevant SAD and MAD data should be reviewed 519 before starting these parts. Deviation from this should always be justified in the protocol." It has not been unusual to include a food effect arm in a SAD study or in parallel with the MAD study, or during a multiple dose study to assess if the IMP might be a perpetrator of DDI (e.g. single dose midazolam) it is considered that this can be done safely as long as appropriately justified (e.g. food interaction in a SAD study at a dose level that has already been well tolerated, is not the maximum dose that has already been studies, and where pre-clinical data indicates that exposure is likely to be reduced with food).	Partly accepted. Text amended.
518-520	30	**Comments:** This sentence is currently imprecise – it is the IMP doses that should not overlap. I.E. the IMP doses used in other study parts with multiple dosing should not exceed those that have already been studied in a MAD cohort. **Proposed change:** Other study parts that involve multiple dosing (e.g. FI and drug-drug interaction) should not use IMP doses that have not already been studied in an earlier MAD cohort.	Not accepted. Too specific detail.
518-520	33	**Comments:** The statement is too restrictive and not consistent with lines just above (514-516) with a more flexible approach, taking	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		into consideration the scientific rationale and the expected exposure which should be equal to or lower than that which was reached in a concluded preceding cohort.	
518-520	47	"Food interaction (FI)" should be deleted from the examples given here as multiple dose designs is not a common design for food interaction studies and might therefore be confusing in light of the previous two paragraphs / bullets. **Comments:** The restriction on parallel MAD cohorts seems unnecessary; guidelines similar to those provided for SAD cohorts would be more appropriate. **Proposed change:** line 518 “Other study parts that involve multiple dosing (~~eg FI or~~ DDI) ~~should not overlap with any earlier~~ could be conducted in parallel with the SAD or MAD cohorts~~.~~, provided the dose and duration chosen and the expected exposures are lower than those attained in a previously concluded MAD cohort where all relevant data has been reviewed and no dose escalation stopping criteria were met”.	Not accepted.
518-520	50	**Comments:** It seems that multiple dosing for FI or DDI studies could follow the same rules that are provide for single-dose and single-dose/multiple-dose overlap. Please allow overlapping multiple dose studies provided that expected exposures have already been tested (and deemed adequately safe).	Not accepted.
518-528	39	**Comments:** We believe that is too conservative and, as in other part of the revised guideline, some flexibility should be offer based on strong scientific rationale (mainly data covering exposure modification possibly associated with food or drug-drug interaction). Need to be consistent across the document (see line 514)	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
521	21	**Proposed change:** We suggest including ethnic factors into the list.	Accepted. Text amended.
521-541	10	**Comments:** The factors for the choice of trial subjects do not include gender and age as selection factors. In addition, it is not mentioned to consider how ill a patient may be or how healthy he/she needs to be to participate in the trial. **Proposed change:** Add gender and age as factors and ask for consideration of the general health status of a patient.	Partly accepted. Text amended.
522-523	18	**Comments:** The list whilst useful it is not exhaustive and it is unclear of its true purpose, is it is a list of healthy volunteer vs patient considerations, or just a list of factors to consider when selecting subjects, if the latter perhaps genotype and ethnic factors could be added. We propose that this factor is added to the current list. **Proposed change:** From The decision to conduct a study in healthy volunteers or patients should be scientifically justified. Factors to consider include: To The decision to conduct a study in healthy volunteers or patients should be scientifically justified.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Factors to consider include: • ethnic factors such as genotype; **Alternative suggestion** From The decision to conduct a study in healthy volunteers or patients should be scientifically justified. To The decision to conduct a study in healthy volunteers or patients, including special populations, should be scientifically justified.	
523-541	47	**Comments:** Consideration should be given to adding to the list of factors to consider novelty of the mechanism of action/target and ability to monitor potential risks **Proposed change:** “Factors to consider include: • the known risks inherent in the type of IMP • the molecular target • the novelty of the mechanism of action/target • ability to monitor potential risks • any long lasting or irreversible pharmacological effect…”	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
529	5	**Comments:** "the *relative* presence of the target in healthy subjects or in patients" **Proposed change:** Differential instead of relative	Not accepted. Too specific detail.
533	5	**Comments:** There is no pharmacological interaction known with excessive exercise	Accepted. Text amended.
533-534	16	**Proposed change:** In addition to lifestyle and medications, I would also consider other comorbid medical conditions	Not accepted. Too specific detail.
535	36	**Comments:** This should include reference to the need to check that healthy volunteers are 'clean' ie from any other trial they may be involved in or have been recently, given that some people are regular volunteers.	Not accepted. Too specific detail.
538	47	**Comments:** It is unclear how predicted therapeutic window of the IMP affects selection of HVs versus patients. Would a narrow therapeutic window favour HVs or patients?	Not accepted. Too specific detail.
538	51	**Comments:** The predicted therapeutic window should be clearly defined, along with all of its synonyms (therapeutic index) and related items (*e.g.,* safety margin). In determining whether to evaluate a compound in healthy volunteers or patients, the safety margin should be taken into account (*i.e.* the ratio of exposure at the animal NOAEL to the predicted exposure in man at each dose level). If the highest dose in healthy volunteers should not be higher than the predicted efficacious	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		dose/exposure, then the ratio at this dose level will be the therapeutic window.	
539-540	9	**Comments:** Consensus needed on defintions/timeframes (3 months, 5xT1/2, ... 3 months after dosing? after last postive PK?) What in case of radioactive labelling. 1-3-5 years may not be necessary for all compounds.	Not accepted. Text deleted.
539-540	9	**Comments:** Better international / European initiative!	Not accepted too specific detail. Text deleted.
539-540	33	**Comments:** European initiatives to prevent over-volunteering should be encouraged.	Not accepted too specific detail. Text deleted.
539-541	16	**Comments:** This is interesting- basically referencing what VerifiedClinicalTrials is doing.	Not accepted too specific detail. Text deleted.
542	25	**Comments:** It is usual to enrol healthy volunteers having safety laboratory values outside of normal ranges but not considered clinically significant. For instance, we see protocols asking for ALT-AST within normal range while others will accept up to 1.5X ULN. A clarification coming from the agency would be appreciated.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
542	47	**Comments:** Indications like e.g. obesity may not really fit with normal ranges; hence relevant to adjust to the normal for "relevant target population". **Proposed change:** Suggest rephrasing: "… trials involving healthy participants should also justify if deviating from normal range of relative risk factors such as weight…"	Partly accepted. Text amended.
542-543	10	**Comments:** Single safety laboratory parameters outside the reference range are the rule rather than the exception even in trials with healthy subjects. This is acceptable as long as this is clinically insignificant and does not compromise interpretation of trial results [Reference: Breithaupt-Groegler K, Coch C, Coenen M et al. Who is a 'healthy subject'? -consensus results on pivotal eligibility criteria for clinical trials. Eur J Clin Pharmacol (2017). doi:10.1007/s00228-016-2189-8]. **Proposed change:** Replace the sentence by "The key inclusion and exclusion criteria for trials involving healthy subjects must be clearly defined and should be appropriate for the chosen population and the type of the trial."	Partly accepted. Text amended.
542-543	16	**Comments:** Not sure I love the language in the last sentence. May be overly picky but this sounds like DMID where we need to be "normal." What is the intent? Can clarification be provided here? **Proposed change:** consider allowing not clinically significant with predefined criteria for acceptable ranges (which may be outside established	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		"normal ranges")	
542-543	22	**Comments:** This statement should be applicable to FIH only, not to all early clinical trials. **Proposed change:** Consider to change wording.	Partly accepted. Text amended.
542-543	22	**Comments:** What is meant by “in line” vs “within”? (“in line” can be interpreted as not clinically relevant? But can be also interpreted that normal ranges are required for all parameters **Proposed change:** Suggested to clarify this statement and to add that “For first in human studies the following essential parameters should be within normal ranges: blood pressure, heart rate, QTc and laboratory data including AST, ALT, creatinine, haemoglobin, and platelets count	Partly accepted. Text amended.
542-543	26	**Comments:** The determination of the normal range is a matter of statistics, e. g. a 90 percentile. Therefore values outside the normal range do not have to be clinically significant and will occur frequently if many parameters are measured. Inclusion / exclusion criteria for healthy volunteers should be allowed to have certain parameters that fall outside normal ranges, if judged to be not clinically significant / acceptable by the investigator. Inclusion and exclusion criteria should take into account the toxicity and safety pharmacology findings from the non-clinical studies and any adverse findings associated with the same pharmacological target and/or drug class. Consequently, ACRO recommends revising the statement. **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Revise the statement to read: " ...should also be in line with the absence of a clinically significant deviation from normal ranges of vital signs…."	
542-543	29	**Comments:** "Normal" ranges are statistically defined and do not *per se* identify pathology when individual values fall outside of the range; even more so when multiple parameters are evaluated. This is usually dealt with in the protocol by relying explicitly on the clinical judgement of the investigator (sometimes supported by discussion with the sponsor medic). It would be worth emphasising this important practical issue to avoid inappropriate exclusions. **Proposed change:** "The key inclusion and exclusion criteria for trials involving healthy participants should ~~**also**~~ be in line with ~~**normal**~~ **reference** ranges of vital signs (including ECG) and safety laboratory values **as judged for clinical significance by the principal investigator**."	Partly accepted. Text amended.
542-543	42	**Comments:** While section 8.2.3 addresses the factors to consider when deciding to conduct a study in healthy volunteers or patients, it was not emphasized that the inclusion and exclusion criteria need to consider the factors addressed in 8.2.3 to ensure the safety of the trial subjects. The draft guideline only requests that inclusion and exclusion criteria should be in line with normal ranges of vital signs and safety laboratory values. **Proposed change:** The key inclusion and exclusion criteria for trials involving healthy participants should address the above factors and be in line with normal ranges of vital signs (including ECG) and safety laboratory values.	Partly accepted. Text amended.
542-543	43	**Comments:** This should also apply to patients to the extent possible.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
542-543	47	**Comments:** Limiting inclusions and exclusion of healthy participants according to those in line with “normal ranges of vital signs and safety laboratory values” does not reflect the fact that some values outside these normal ranges may not be clinically significant. **Proposed change:** “The key inclusion and exclusion criteria for trials involving healthy participants should reflect clinically significant deviations from normal ranges of vital signs (including ECG) and safety laboratory values”	Partly accepted. Text amended.
542-543	50	**Comments:** Normal ranges vary from laboratory to laboratory and values within an individual can fluctuate from day to day. Deviations from normal will inevitably occur in later phase trials and determination of safety of an IMP in this context is best done in a well-monitored Phase 1 setting. Please allow clinical judgement to determine if out-of-range values are allowable.	Partly accepted. Text amended.
543	45	**Comments:** Suggested clarification **Proposed change:** Change from “….and safety laboratory values” to “…and **relevant** laboratory values.”	Partly accepted. Text amended.
544	3	**Comments:**	Not accepted. Outside current

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		The EMA Guidance specifies that: “The practice of conducting FIH/early CTs with integrated protocols means that the information generated in previous parts needs to be analysed and integrated into an assessment in a limited timeframe as defined in the protocol prior to making a decision on proceeding to the next part.” **Proposed change:** In line with RSS recommendations, may I suggest that the extent of approvals for integrated protocols in the years since TGN1412 in 2006 be documented by EMA, ANSM, MHRA and their European counterparts.	scope.
544-563	40	**Comments:** Would it be worth including in this section that the protocol should specify the required follow up data from subjects within a cohort before the dose escalation meeting and decision can be made. More detail is included in Section 8.2.7, but it may also be applicable to include in this section.	Partly accepted. Text amended.
545-548	17	**Comments:** It’s not clear what the difference is between ‘subject safety assessments that will be routinely conducted’ and ‘additional monitoring actions’, both of which must be pre-specified and justified in the context of the pharmacology and toxicology of the IMP. **Proposed change:** Please clarify.	Partly accepted. Text amended.
545-549	42	**Comments:** Section 8.2.4 appears to address safety assessments only after IMP application, while baseline safety assessments are not specified. **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Add between first and second sentence in section 8.2.4: <u>Baseline safety assessments should be performed before IMP application.</u>	
545-552	47	**Comments:** Consideration should be given to adding a comment on availability of intervention therapies where applicable? For example if hypersensitivity is an expected and particular concern, early trials may include pre-treatment with or immediate availability of anti-histamines etc until more experience in the clinical effect has been gained. **Proposed change:** "The subject safety assessments that will be routinely conducted and any additional monitoring actions should be pre-specified and justified in line with the known non-clinical and pharmacological profile. Where appropriate for the target or drug substance class, interventional treatments and/or prophylactic medication should be specified and made available during the dosing period. There should also be routine general monitoring to detect potential unexpected adverse effects that are not related to known properties of the IMP (e.g. vital signs, ECG, respiratory signs and symptoms, clinical lab values or general neurological assessment, physical examination and interview). Repeated assessments, integrating all available pharmacological, PK, PD and toxicological knowledge, and rapid processing of this information are crucial for the recognition and interpretation of developing toxicity at an early or potentially reversible stage."	Partly accepted. Text amended.
545-554	17	**Comments:** The requirements in section 8.2.4 for pre-specifying planned assessments and interventions are repetitive. **Proposed change:** Add the following to the start of section 8.2.4: '**<u>All planned assessments and interventions should be clearly pre-specified.</u>**' Then delete from line 546 'pre-specified and', and delete the first sentence of the second paragraph (lines 553–554).	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
547-549	42	**Comments:** While the need to establish baseline VS prior to IMP administration would appear to be self-evident (see section discussed) there have been protocols written that only require VS following IMP administration. **Proposed change:** Recommend spelling out the need for baseline safety evaluations prior to IMP administration be spelled out.	Not accepted. Too specific detail.
549	21	**Comments:** General neurological assessment is part of a physical examination and interview. It should not be singled out amongst the other assessments. **Proposed change:** We suggest deleting the term “general neurological assessment**”.**	Not accepted. Too specific detail.
549-552	9	**Comments:** It will not always be feasible to have PK and especially PD results without significant impact on timelines	Partly accepted. Text amended.
551-552	47	**Comments:** It is not clear why there is specific emphasis on “toxicity at an early *or potentially reversible* stage”, as toxicities should be detected as early as possible independent of reversibility.	Accepted. Text amended.
553-556	3	**Comments:** In Section 8.2.4, the EMA Guidance should differentiate between the timing when assessments are made and the waiting-time until the results are received on the assessments made (lines 553-556). Please see RSS recommendations.	Not accepted. Too specific detail.
554-	21	**Comments:**	Not accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
556		An adaptive CT protocol allows for adaptability of nature, timing and frequency of assessments, based on emerging data. The protocol should specify the minimum requirements and maximum adaptability, rather than exact nature, timing and frequency, which may prove inappropriate or inadequate, once the first human data becomes available. Furthermore, rather than cluttering a protocol with detailed descriptions of assessments, it should be permissible to describe detail in operational manuals outside the protocol. **Proposed change:** To amend the text as follows: "The ~~exact~~ nature of the proposed assessments and their **anticipated** timing should be provided **in the CT protocol. The CT protocol should also provide the proposed adaptability of timing, frequency and nature of the assessments and the minimum requirements in relation to these assessments.** Any subsequent proposal **to reduce the minimum requirements** should be justified, such as if a finding in non-clinical data is shown to be animal specific."	Too specific detail.
553-556	45	**Comments:** Paragraph does not refer to (or apply to) 'interventions', although 'interventions' are mentioned in first sentence. **Proposed change:** Delete "~~and interventions~~," in line 553	Accepted. Text amended.
557-578	51	**Comments:** For the first SAD cohort sentinel dosing may be appropriate dependent on the risks as described in section 4, but not necessarily for all cohorts. This also seems to be implied in lines 590-593. **Proposed change:** Sentinel dosing in the first single dose cohort should be discussed. If warranted, it should be also justified how many	Partly accepted. Text relating to sentinel dosing amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		cohorts may use this sentinel dosing. Relevance of sentinel dosing in the multiple dose studies may be a point of discussion when warranted.	
558	17	**Comments:** State that the sponsor will *pre-specify* extension of safety monitoring. **Proposed change:** The sponsor should **specify and** justify how safety monitoring should be extended….	Partly accepted. Text amended.
558	30	**Comments:** 'Justify' is not the right word – of course safety monitoring of any subject would/should be extended until parameters return to normal/baseline; and it should be in the protocol. **Proposed change:** The protocol should describe how safety monitoring should be extended…	Partly accepted. Text amended.
558-559	47	**Comments:** Deviations from normal range /baseline are very common for safety parameters. Therefore, termination of further follow-up should also be allowed upon return to an acceptable level. **Proposed change:** "…until parameters return to within the normal range / baseline or an acceptable level."	Partly accepted. Text amended.
559	9	**Comments:** Better: "until not clinically significant" (iso "to within the normal range or to baseline")	Not accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
560	47	**Comments:** The reviewer appreciates that this sentence only lists examples, but recommends to not limiting it to enzyme inhibition but also considers enzyme activation. **Proposed change:** Other examples of when extended monitoring should be considered to include when the mechanism entails enzyme inhibition/activation (or: modulation of enzyme activity)….	Partly accepted. Text amended.
563-564	38	**Comments:** Because this guideline is going to be revised considering the event of BIA 10-2474, we would like to propose that the following point should be added to the last part of item 8.2.4. “Subject assessment and intervention”. This point has not been discussed by the ASNM-TSSC designated by the French Ministry. Both of ASNM-TSSC and Kerbrat, et al (NEJM 2016) simply ruled out causality between endcannabinoid system and cerebral bleeding, however, we would like to request experts to discuss on this point, as one of the hypotheses. We are preparing a paper on this point to be published at the end of April. **Proposed change:** (The following description should be added to the last part of the item 8.2.4. “Subject assessment and intervention”.) When the candidate drug has a potency of altering hemostasis ability or biophylactic system, e.g., endocannabinoid system, clinical laboratory test on bleeding tendency should be placed, if appropriate.	Not accepted. Too specific detail.
564	9	**Comments:** What about guidance on escalation within cohorts in SAD (eg cohort A and cohort B alternate dosing scheme => less volunteers exposed but more carry-over effects possible)	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
564	9	**Comments:** The way the guideline is written seems to imply that for each next dose a new cohort of subjects is recruited. However, dose selections are also often done within one cohort (e.g. 2 alternating cohorts which are each dosed in 4 alternating periods). Is it really the intention of the guideline not to allow different dose levels in one group so that for each dose level another group of volunteers would be needed? We assume that the text should be adjusted to allow this flexibility of dosing more then once within a group.	Accepted. Text amended.
565-566	30	**Comments:** Little guidance is offered about what to do when PK/PD variability is noted within a cohort. Suggest advice to expand the cohort and/or the next cohort. A substantial amendment is likely to be required. **Proposed change:** The number of subjects per dose increment (the cohort size) depends on the variability of both PK and PD parameters and the trial objectives such as justifying progression to the next cohort. If high variability in PK/PD occurs in any cohort, this cohort should be enlarged to gain better understanding of variability (or the same dose studied in a subsequent cohort).	Not accepted. Too specific detail.
565-566	40	**Comment:** In oncology, the number of subjects can also depend on the target maximal toxicity.	Not accepted. Too specific detail.
565-566	51	**Comments:** At the time of designing the FIH clinical trial it is not possible to predict the variability in exposure or PD response in man. It is most often assumed that the variability in man will be similar to that in animals. PD data are reported and interpreted differently to PK data (*i.e.,* Cmax and AUC are calculated for PK but Emax and AUEC are not routinely reported). For PD data, duration of effect is more commonly used. It is not clear how the sample size relates to the	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		decision to progress to the next dose cohort.	
565-570	20	**Comments:** Flexibility regarding number of cohorts is specifically mentioned, but not regarding the number of subjects per cohort (cohort size). Typically, number of subject per cohort is based on the need for safety assessment. PK and PD for new drug candidates can range outside anticipated projections or demonstrate considerable variability. In these cases it is advantageous to build in flexibility to expand a cohort size to better characterize the findings at a given dose level. **Proposed change:** “The number of subjects per dose increment (the cohort size) depends on the variability of both PK and PD parameters and the trial objectives such as justifying progression to the next cohort, and may change across cohorts as data emerges, as pre-specified in the protocol.”	Not accepted. Too specific detail.
565-570	47	**Comments:** Flexibility regarding number of cohorts is specifically mentioned, but not regarding the number of subjects per cohort (cohort size). Typically, number of subject per cohort is based on the need for safety assessment. PK and PD for new drug candidates can range outside anticipated projections or demonstrate considerable variability. In these cases it is advantageous to build in flexibility to expand a cohort size to better characterize the findings at a given dose level. **Proposed change:** “The number of subjects per dose increment (the cohort size) depends on the variability of both PK and PD parameters and the trial objectives such as justifying progression to the next cohort, and may change across cohorts as data emerges, as pre-specified in the protocol.”	Not accepted. Too specific detail.
565-573	33	**Comment 1:** SAD design using rotating panels is not taken into consideration. Alternating cohorts of subjects can be dosed in	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		alternating periods, e.g. cohort A is dosed with dose 1, then cohort B is dosed with dose 2, then cohort A is dosed with dose 3… **Comment 2:** Flexibility for the number of subjects per cohort as well as cohort repetition is particularly relevant when using Bayesian approaches with Continuous Reassessment Method (CRM), provided a strong pre-specified rationale and rules. **Comment 3:** Repetition should be possible even at the current dose level (if stopping rules are not reached).	detail.
567	20	**Comments:** While predicted exposures could be provided for every dose cohort in the protocol, it may not be meaningful as clinical exposures are often significantly different than predictions. Such projections could be misleading or provide a false sense of confidence in the PK and dose predictions. It would be more practical to provide the predicted exposure for the first dose cohort, the projected therapeutic exposure range, and the maximum exposure level, acknowledging dose escalation must be in response to emerging PK data.	Not accepted. Too specific detail.
567-568	17	**Comments:** Owing to the difficulty of predicting human exposure from animal data, there should not be a requirement for each dose level to be pre-specified in the protocol. The starting dose must be specified and justified, and it should be acceptable for subsequent doses to be determined based on emerging data and pre-specified dose selection criteria. **Proposed change:** A maximum number of cohorts that will be dosed **and the starting dose** ~~and the corresponding doses with the expected exposure for each cohort~~ should be stated in the protocol. **The protocol should also specify the subsequent dose levels to be tested (with the corresponding expected exposures) and/or dose selection criteria.**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
567-568	18	**Comments:** This text suggests that it is mandatory to state the doses and corresponding exposure for each cohort. Whilst planned doses can often be stated, it is common to determine actual doses based on the data review from the preceding cohort. Stating planned doses in the protocol and then actual doses in the clinical study report can lead to confusion. Similarly, whilst expected exposure may be able to be stated this has the potential to cause confusion once actual data emerge, which may be different from expectation. We propose that the requirement should be for starting dose, dose escalation criteria and maximum exposure to be stated. **Proposed change:** From A maximum number of cohorts that will be dosed and the corresponding doses with the expected exposure for each cohort should be stated in the protocol. To A maximum number of cohorts that will be dosed and the starting dose, dose escalation criteria and maximum exposure for each cohort should be stated in the protocol.	Partly accepted. Text amended.
567-568	47	**Comments:** We agree that an adequate prediction of the human exposure is an important aspect in planning for the number of cohorts and doses planned in a trial. Having an exposure estimate for each cohort in the protocol would also bring into question as to how much is the deviation from the prediction in the protocol possible and also the consequences of being off by a certain amount. Would protocol have to be amended each time the protocol prediction is off by a certain percentage? The exposure at the pharmacologically active dose (PAD) levels and NOAEL is predicted and kept in mind when preparing a FIH study protocol. Based on these predictions a substantial safety margin is planned and a frequent monitoring of the exposure with ascending dose steps and a stringent safety monitoring at each dose step is performed to	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		ensure the safety of the participants. **Proposed change:** A maximum number of cohorts that will be dosed and the corresponding doses with the distance/margin to the PAD and NOAEL for each dose should be stated in the protocol.	
567-568	47	**Comments:** Doses beyond starting dose should be dynamic and depend on safety/PK information generated in prior cohorts, within a predefined maximum exposure boundary. Max escalation steps are to be defined instead.	Partly accepted. Text amended.
567-568	47	**Comments:** Similar to comment for lines 345, the requirement to justify PK estimates for the in-between doses are not useful and seem too much. **Proposed change:** Suggest focus on starting and maximum and therapeutic dose levels	Partly accepted. Text amended.
567-568	51	**Proposed change:** A planned maximum number of cohorts that will be dosed and the corresponding doses with the expected exposure for each cohort should be stated in the protocol.	Partly accepted. Text amended.
567-570	47	**Comments:** Lines 567-568 seem to conflict with 569-570. **Proposed change:** Consolidate lines 567-568 together with lines 569-570 by clarifying that fewer than the maximum predefined number of	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		cohorts may be investigated, or delete lines 567-568.	
567-570	50	**Comments:** Lines 567-568 seem to conflict with lines 569-570. **Proposed change:** Consolidate lines 567-568 together with lines 569-570 by clarifying that fewer than the maximum predefined number of cohorts may be investigated, or delete lines 567-568.	Partly accepted. Text amended.
569-570	39	**Comments:** Flexibility for the number of subjects per cohort as well as cohort repetition should be allowed, this is particularly relevant when using Bayesian approaches with Continuous Reassessment Method (CRM), again with all pre-specified rationale and rules	Partly accepted. Text amended.
571-572, 586, 602-603, 652, 659	21	**Comments:** See above comment regarding stopping rules **Proposed change:** To amend the term “stopping rules/criteria” to **“toxicity/stopping rules/criteria”.**	Not accepted. Too specific detail.
571-573	47	**Comments:** If dose-escalation stopping rules are not met, the Sponsor should be allowed to repeat the same dose in another cohort. **Proposed change:** “~~It is not acceptable to allow repetition of a dose level or cohort where that dose has met any of the dose escalation~~	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		~~stopping rules (see section 8.2.10.).~~ If dose-escalation stopping rules are not met, repetition of a dose level (or lower or intermediate dose level) would be acceptable and this should be clearly indicated."	
571-573	43	**Comments:** This is not fully applicable to some model-guided adaptive dose-escalation used in oncology FIH studies. For example, enrolment of an enrichment cohort at a previously tested dose level is stopped if 2 patients experience a dose limiting toxicity (DLT) (e.g., a total of 8 patients are treated on this dose level with 2 DLT observed). Enrolment in this cohort may resume if supported by the available data (including modelling of DLT). Alternatively, a new cohort of patients may be recruited to a lower dose and re-escalation may occur if data in subsequent cohorts support it. Such situations should of course be clearly and prospectively described in the protocol. **Proposed change:** Add after L. 573 "If repetition of cohorts is allowed it should be prospectively indicated in the study protocol. Typically only lower or intermediate dose level cohorts would be acceptable, but there can be exceptions in certain settings if appropriate methodology is prospectively defined in the study protocol."	Not accepted. Too specific detail.
572	9	**Comments:** Please specify that this refer to STUDY stopping rules	Not accepted. Too specific detail.
572-573	17	**Comments:** The following text is unclear: 'If repetition of cohorts is allowed in the protocol then only a lower or intermediate dose level would be acceptable and this should be clearly indicated.' The preceding sentence is clear enough in stating that a dose level that has met stopping rules must not be repeated even if the protocol allows repetition of dose levels. **Proposed change:**	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		~~If repetition of cohorts is allowed in the protocol then only a lower or intermediate dose level would be acceptable and this should be clearly indicated.~~ **If the protocol allows repetition of dose levels, it must clearly state that any dose level that has met the dose escalation stopping rules must not be repeated.**	
572-573	39	**Comments:** Repetition should be possible even at the current dose level (if stopping rules not reached)	Not accepted. Too specific detail.
572-573	47	**Comments:** It should be clarified that the last sentence of the paragraph only refers to sentence one. Otherwise the second sentence should be amended at the end by "unless justified". Repetition of dose steps with the same dose may be justified for non-safety reasons, eg to extend the database on PD endpoints or biomarker while proceeding with the dose escalation in the absence of any safety concern.	Not accepted. Too specific detail.
574-593	17	**Comments:** This section is unclear. If 'cohort' here means 'dose level' (see general comments above), the first paragraph of this section explicitly requires sentinel subjects at every new escalating dose level. However, the final paragraph contradicts that paragraph, as it says "This approach *may also be appropriate* at later stages of study design, e.g. on the steep part of the dose response curve…" etc – the implication being that it's not necessary to use sentinel subjects at every dose level. Many first-in-human SAD protocols specify use of sentinel subjects for the starting dose, but not for subsequent dose levels. Using that approach, dose escalation in SAD trials has an excellent safety record, and it should be possible to allow dose *escalation* beyond the first dose without use of sentinel subjects if that can be justified. In first-in-human SAD studies, it is not unusual to test escalating doses initially, then to de-escalate – perhaps retesting some dose levels or exploring new intermediate dose levels. So, during the course of a SAD study, dose levels can go	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		down as well as up. The same can be true of MAD studies. Please clarify that sentinel dosing is required only for new *escalating* doses – if the chosen dose level for the next treatment period does not exceed a dose level already shown to have acceptable tolerability, sentinel subjects are not required. It's unclear whether the Guidance recommends sentinel dosing in MAD studies. Since we don't understand what went wrong in the Bial trial in France, it doesn't make sense to change established practice, which, with the exception of the Bial trial, has an excellent safety record. Requiring sentinel dosing at every dose level in a MAD study would substantially increase the time needed to complete early clinical trials, and delay patients' access to a potentially useful new medicine. Sentinel subjects should be considered, but should not be a requirement. **Proposed change:** Clarify that sentinel subjects are needed only when the dose is escalated. Clarify that sentinels should be used for the starting dose but may not be required at every escalating dose level in SAD studies. Specify that sentinel dosing may not be required in all MAD studies.	
574-593	20	**Comments:** This section lacks clarity on when the use of sentinel subjects is recommended, including which cohorts and study parts. The text in lines 590-593 ("This approach may also be appropriate at later stages of study design, e.g. on the steep part of the dose response curve…") suggests that sentinel subjects are not compulsory for all cohorts, but seems to contradict the statement on line 575: "… first dose in any cohort …" We recommend the guidance make clear that use of sentinel subjects should be case-by-case and program driven, with appropriate justification (eg. high level of precedence and known or benign pathway). The time interval between sentinels and the remaining cohort should not be arbitrary but based on the PK/PD/safety profile with the protocol containing language for adjustments to these intervals based on emerging clinical data. **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		In some cases, it is considered appropriate to design the administration of the first dose in any cohort so that one or more subjects receive a single dose of the active IMP. When the study design includes the use of placebo it would be appropriate to allow for subjects on active and as well as placebo to be dosed simultaneously prior to dosing the remaining subjects in the cohort. Some novel IMPs may require this precaution over and above the first dose in a cohort, if MOA / population or other specific issues warrants. In other instances, it may not be required and should therefore be justified in the IB and/or protocol, including any relevant monitoring needed in accordance with toxicity findings.	
575	3	**Comments:** In Section 8.2.6, the EMA Guidance appears to suggest that a single sentinel pair (active; placebo) per cohort is sufficiently precautionary. Please see RSS recommendations to the contrary and note that (line 575) “in any cohort” should probably read “in every cohort” to convey more accurately the suggestion that the EMA Guidance makes. **Proposed change:** As above.	Partly accepted. Text amended.
575	9	**Comments:** What about MAD staggered dosing rules and stopping rules?	Partly accepted. Text amended.
575	25	**Comments:** Does that imply a formal need for sentinels not only in single dose cohorts, but also in multiple dose cohorts ? We believe accumulation, specificity, PK data etc. are to be assessed and to determine whether the presence of sentinels in Multiple dose cohorts is appropriate. **Proposed change:** Addition:	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		For MAD, not including sentinel cohort should be well justified in the protocol.	
575	30	**Comments:** Make explicit that this relates to both SAD and MAD cohorts and to ALL cohorts. However, allow some flexibility to limit numbers exposed in the sentinel group without specifying that it is exactly one e.g., dose 2 active and 1 placebo and if data are incomplete in one subject, allow continuation if data available on at least 2 (1 active and 1 placebo). The size of the sentinel groups should depend on SAD and earlier MAD cohorts. **Proposed change:** It is considered appropriate to design the administration of the first dose in all SAD or MAD cohort so that usually a single subject receives a single dose of the active IMP. The precise number selected, and the delay before subsequent dosing, should be determined after analysing all information collected from earlier cohorts.	Partly accepted. Text amended.
575-576	9	**Comments:** Is sentinel dosing an obligation for all dose levels?	Partly accepted. Text amended.
575-576	18	**Comments:** Please can clarification of this text be provided. Is it meant to suggest that sentinel dosing is required for all cohorts, or that it could be applied to any cohort dependent on a scientific review of data? We assume the latter given that sentinel dosing for all cohorts is not always justified and that lines 590-593 state that sentinel dosing may also be appropriate at later stages of the study design. **Proposed change:** From: It is considered appropriate to design the administration of the first dose in any cohort so that a single subject receives a single dose of the active IMP. When the study design includes the use of placebo it would be appropriate to allow for one	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		subject on active and one on placebo to be dosed simultaneously prior to dosing the remaining subjects in the cohort. To: Sentinel dosing is the administration of the first dose so that a single subject receives a single dose of the active IMP in advance of the remaining subjects in a cohort. When the study design includes the use of placebo it would be appropriate to allow for one subject on active and one on placebo to be dosed simultaneously prior to dosing the remaining subjects in the cohort. It will usually be appropriate to conduct sentinel dosing for the initial cohorts of a FIH study, for example until quantifiable systemic exposure has been confirmed. The plan for sentinel dosing should be defined in the study protocol.	
575-576	21	**Comments:** This statement implies that sentinel dosing is mandatory for any escalating single dose cohort. Whilst this may be appropriate in many circumstances and for many IMP, sentinel dosing may not always be appropriate or required. We propose that the absence of sentinel dosing should be permissible, if justified. **Proposed change:** To amend the text as follows: It is considered appropriate **for many IMPs** to design the administration of the first dose of any escalating single dose cohort so that one single subject receives a dose of the IMP. When the study design includes the use of placebo it would be appropriate to allow for one subject on active and one on placebo to be dosed simultaneously prior to dosing the remaining subjects in the cohort. **Whenever this approach is not proposed, the CT protocol should provide justification.**	Partly accepted. Text amended.
575-576	27	**Comments:** Sentinel dosing is an important safety mechanism to ensure that the number of patients exposed to a novel chemical entity is limited when there may be an increased risk of adverse reaction. This risk is not uniform across cohorts in a	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		First-In-Human study, and should be implemented when scientifically justified. **Proposed change:** It is considered appropriate to consider designing the administration of the first dose in a cohort so that a single subject may receive a single dose of the active IMP, e.g. on the steep part of the dose response curve, when approaching target saturation levels or exposure margins to non-clinical NOAELs, in case of non-linear PK, or in light of emerging clinical signs or adverse events that do not meet stopping criteria.	
575-576	37	**Comments:** We suggest that this section be expanded to include recommendations in relation to the use of sentinel dosing for MAD cohorts.	Partly accepted. Text amended.
575-576	41	**Comments:** It should be made clear here that “any cohort” includes SAD and MAD cohorts (and any other cohorts incorporated in the study design) in relation to the first dose being given to a single participant.	Partly accepted. Text amended.
575-578	14	**Comments:** The practice of sentinel cohorts is well-established and may be appropriate in some cases, but will not identify risks with low incident rates and has a low predictive value – for example, the power of detecting an adverse drug reaction occurring in 30% of subjects exposed to active drug is only about 13% in a typical 6+2 design, and obviously even lower in a sentinel cohort of 1+1; conversely, detecting a rare event (occurring in <10% of subjects) would require group sizes not compatible with ethics or the objectives of a FIH study. Attempts to reduce risk to near-zero will compromise the value of the study and any false positives will lead to less potentially efficacious drugs being progressed to testing in patients. **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Suggest introducing the following text (or other suitable language to this effect): “When assessing data from such so-called sentinel cohorts, it should be borne in mind that results deriving from one or two subjects per cohort have low statistical power to identify adverse drug reactions and decisions to include the rest of the cohort should be based on assessment of all available data using a weight-of-evidence approach.”	
575-578	16	**Comments:** I agree with this if it is a FIH study, where there is no human data to draw upon. There may be exceptions which aren't specified here currently - food/drug interaction studies where the PK/safety has already been established at the dose/exposure planned in another cohort, bioequivalence studies, new formulations where expected exposures can be reasonably predicted. The way it is now seems vague and could be interpreted to mean all cohorts of all phase 1 studies. Interim PK analyses between cohorts may also be useful for ensuring predicted vs observed exposures. If predictions are accurate then may be reasonable to dose multiple subjects where expected exposures in next planned cohort has previously been shown to be safe. Alluded to below in next section (8.2.7)	Partly accepted. Text amended.
575-578	23	**Comments:** Preferred to keep original text from current guideline ‘It is usually considered’. Sentinel dosing is generally justified for e.g. immune suppressants or biologicals, but would be an overkill for the vast majority of small molecules that can be categorised as low risk. A too stringent enforcement will slow down development. Instead it is proposed that the classical thorough risk assessment (MOA, molecule properties, safety signals, safety windows …) defines whether sentinel dosing is mandated, instead of making it a standard expectation. Especially when testing one placebo vs one IMP, this might lead to stopping the study based on a premature dataset (linked to next point, lines 672-676). **Proposed change:** “It is **<u>usually</u>** considered appropriate to design ….”	Partly accepted. Text amended.
575-	29	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
578		"It is considered appropriate to design the administration of the first dose in any cohort so that a single subject receives a single dose of the active IMP. When the study design includes the use of placebo it would be appropriate to allow for one subject on active and one on placebo to be dosed simultaneously prior to dosing the remaining subjects in the cohort." This "sentinel dose" strategy is (wisely) currently widely adopted. However, many protocols currently exist where this strategy is applied only to the first (lowest) dose level (ie literally the "first-in-man" dose) – it would be worth stressing that it should apply to every incremental dose level.	Text amended.
575-578	39	**Comments:** The used of sentinel subject should be clarified: is it for all cohorts? Is it for SAD as well as MAD or even ancillary studies (drug-drug interaction, Food interaction)? We propose to keep the sentinel subjects for SAD only and even more only the first dose level (based on the appropriate rationale). For the MAD nothing is clearly written, we suggest to not introduce the concept of sentinel subject (as in the current guideline). But splitting the MAD cohorts into 2 or 3 subgroup could be suggested as it is very appropriate to mitigate the risk.	Partly accepted. Text amended.
575-578	43	**Comments:** It is unclear if staggered enrolment / observation periods are considered appropriate for dose escalation in the oncology setting. In any case, the need for sentinel dosing should be flexible as in certain instances staggered dosing may not be warranted.	Partly accepted. Text amended.
575-578	47	Scientific basis for sentinel dosing **Comments:** A blanket requirement for sentinel or staggered dosing in every cohort at every dose level with a standardized design across all cohorts in all studies may be unnecessary, unscientific, and ultimately unhelpful. Sentinel and staggered dosing strategies should be scientific, risk-based, and tailored to the specific situation. Points to consider when devising the	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		specific design of a sentinel cohort or staggered dosing strategy include biostatistical factors (expected frequency of SAEs and the sample size), the pharmacologic relevance of a given exposure (e.g., receptor occupancy), inter-individual variability (e.g., baseline characteristics, exposure differences, metabolism differences, variability in the PD effect), the PK/PD relationship, the target biology, the potential for hysteresis, and the potential for off-target effects. The vast majority of the time, the practice of conducting a sentinel dose will reveal no significant safety findings or adverse events (no serious adverse events [SAEs]). Without the rest of the cohort (or other cohorts) or placebo to compare to, there is limited information to interpret the significance of the adverse event (whether it is drug related). Potentially, if the conservative approach is taken, a number of drugs may be inappropriately terminated in Phase 1 due to random AEs in single sentinel doses that are not drug related. On the other hand, if only serious adverse events are flagged, the problem of a low positive predictive value only worsens. Given that sensitivity should be high (low false negative rate so we don't miss dangerous drugs), the specificity must decrease given the nature of most tests and the ROC model. Further, if the prevalence (prior probability) of a drug in non-oncology Phase 1 clinical trials causing an SAE is low (<1%) the positive predictive value [PPV] (True positives [TP]/TP + false positives [FP]) of the test becomes drastically reduced. If the PPV is very low, either drugs are killed inappropriately, or there becomes the issue of 'crying wolf', when a positive signal is not believed, as it is more likely to be a false positive than a true positive. Therefore, utilization of where a compound lies on a continuum of risk is critically important in the design of a trial. The likelihood of a sample size of 1 yielding data which is interpretable needs to be assessed prior to instituting a sentinel dose. If the drug has a reasonable potential in stimulating a large safety signal versus noise, a sentinel dose may be helpful. For example in case of unpredictable translation to human in combination with clear safety risks from toxicology data/ or on target PD. This is unlikely to be common. **Proposed change:** ~~It is considered appropriate to design the administration of the first dose in any cohort so that a single subject receives a single dose of the active IMP. When the study design includes the use of placebo it would be appropriate to allow for one subject on active and one on placebo to be dosed simultaneously prior to dosing the remaining subjects in the cohort.~~	

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		"Sentinel dosing, where a single subject receives a single dose of the active investigational medicinal product (IMP) prior to the rest of the cohort, should be considered for inclusion predicated on a risk-based, totality of evidence approach. Sentinel dosing should be applied to SAD and MAD trial designs where the prior probability of risk is large enough that a dose may be associated with an SAE, so as that the positive predictive value of the single subject/patient will be likely to yield a true positive result. Accordantly, a lower risk compound would be best served by data from a full cohort before decisions are made on dose escalation. This risk is dependent on the NME mechanism of action, potential target, cascade activation potential, toxicology, etc. (see section of risk continuum)."	
575-578	50	<u>Scientific basis for sentinel dosing</u> **Comments:** Because significant human toxicities can be difficult to predict accurately from non-clinical models, we agree that sentinel dosing and/or staggered dosing, if implemented in a thoughtful manner, can reduce risk in first-in-human studies. However, a blanket requirement (or "one size fits all" approach) for sentinel or staggered dosing in every cohort, at every dose level, with a standardized design across all studies, with all types of investigational molecular products (e.g., one subject to receive active drug as described in lines 576-577) may be unnecessary and ultimately unhelpful in reducing risk. In fact, if the sentinel is not designed with consideration of the anticipated PK or the pharmacology or the pattern of safety issues of concern, it is quite possible to be falsely reassured by a "clean" single sentinel subject after a defined period of observation, especially if exposures will continue to increase after an observation period (i.e., if the sentinel observation period ends before steady-state is achieved) or if serious adverse events do not occur in all exposed subjects in the same manner (i.e., if some subjects have a delayed response or less severe adverse events). In addition, the strategic determination to apply a sentinel approach must take into consideration the various kinds of investigational medical products (small molecules, antibodies, antibody-drug-conjugates, cytokines, etc.). Therefore, sentinel and staggered dosing strategies should be scientific, risk-based, and tailored to the specific situation. One potential problem with sentinel dosing and the possibility of false reassurance is illustrated with the following. The concept of Number Needed to Harm, i.e., NNH = 1/(prob_exposure-prob_nonexposure) = 1/ (absolute risk increase above background) tells	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		us that a sentinel group of one on active and one on placebo can only detect AEs with a high probability of occurrence. For example, if the true frequency of SAEs is 100% in exposed subjects, as with TGN1412, then a sentinel group of one will be effective since the NNH=1. However, if the true frequency of SAEs is 50%, which is still unacceptably high, then the NNH would be 2, i.e., on average, two or more subjects would need to be dosed for one to have an SAE. In such a case, a "clean" sentinel could be falsely reassuring. Bayesian adaptive designs represent a supplementary approach to sentinel dosing that can further reduce the chance of dosing individuals at a non-tolerated dose. Dose-escalation increments are based on the prediction of the percentage of dose-limiting adverse events expected at the next dose level, based on accumulated experience. Bayesian adaptive designs show a good performance in the estimation of MTD and in reducing the total number of HVs exposed. Some points to consider when devising the specific design of a sentinel cohort or staggered dosing strategy should include variables that could significantly affect the likelihood of the sentinel cohort of detecting toxicity. These include: • Biostatistical factors (i.e., the expected frequency of SAEs and the sample size, since low frequency events will be unlikely to occur in one sentinel subject • The pharmacologic relevance of a given exposure (e.g., receptor occupancy), since a low receptor occupancy state will have a lower probability of a drug-related adverse event than a high receptor occupancy state • Inter-individual variability (e.g., baseline characteristics, exposure differences, metabolism differences, variability in the PD effect), since adverse events can present differently in different individuals • The PK/PD relationship • The target biology • The potential for hysteresis of serious toxicities • The potential for off-target effects. **Proposed change:** ~~"It is considered appropriate to design the administration of the first dose in any cohort so that a single subject receives a single dose of the active IMP. When the study design includes the use of placebo it would be appropriate to allow for one~~	

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		~~subject on active and one on placebo to be dosed simultaneously prior to dosing the remaining subjects in the cohort.~~ ***Sentinel or staggered dosing is a risk-mitigation strategy that should be considered in certain situations, both in single and multiple dose studies, in order to reduce the risks associated with exposing all subjects in a cohort simultaneously. The protocol should justify when and how sentinel dosing is to be used and should also describe the scientific rationale for the specific design of the sentinel strategy. Sentinel dosing may be appropriate at all doses or only at the doses where the risk of significant toxicities may be increased, such as the first dose administered to healthy volunteers or the first dose administered to a population that may be particularly vulnerable to certain toxicities. Other scenarios may also lead to implementation of sentinel or staggered dosing: when receptor occupancy is expected to be high, when off-target effects might be more likely, when doses are considerably higher than the expected therapeutic dose, when a pattern of clinical findings emerges and is divergent from nonclinical toxicology results, when the safety margin (e.g., calculated from the NOAELs in nonclinical studies) is narrow, or when one or more subjects has experienced a safety or tolerability issue that would be unacceptable if it occurred more frequently or more severely in subsequent cohorts. If sentinel dosing is not planned for one or more cohorts, justification should be provided in the protocol. Furthermore, Sponsors should realize that sentinel dosing can reduce risk but will not eliminate risk to subsequent subjects.*** ***In addition to sentinel dosing, the use of Bayesian adaptive dose escalation designs should be considered where prior information and data from all dose levels are used to estimate the probability of adverse events at future doses. This is used to guide the choice of the next dose level. Cohort sizes can be small initially and increased at doses expected to be most informative such as those in the linear portion of the dose-response curve for pharmacology or those that are close to a pre-determined level of unacceptable adverse events."***	
575-593	3	**Comments:** Because serious adverse events may not occur uniformly, as in BIAL trial to only a third of actively treated subjects in MAD cohort 5 on their 5th day of exposure, Section 8.2.6 should highlight more precautionary designs. Consider, for	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		example, nine persons per cohort who, in cohort X, are randomized to three sub-cohorts and to active(A) versus control/placebo as follows: Sub-cohort 1 in cohort X= a pair, randomized to A versus control/placebo Sub-cohort 2 in cohort X= a triple, randomized to A & A versus control/placebo Sub-cohort 3 in cohort X= a quartet, randomized to A, A, A versus control/placebo. Each sub-cohort has a subject randomized to control/placebo to aid masked assessment. But, there are two precautionary steps (sub-cohorts 1 & 2) by which protection is afforded to half the subjects randomized to A. There is, however, still a 1 in 8 chance that a serious A-related adverse event that affects half the subjects randomized to A would not arise in sub-cohorts 1+2.	
575-593	49	**Comments:** Section 8.2.6 (lines 575-593) should highlight more precautionary designs, because serious adverse events may not manifest themselves in all participants at the same speed. **Proposed change:** line 575 “in any cohort” should probably read “in every cohort” to convey more accurately the suggestion that the EMA Guidance makes	Partly accepted. Text amended.
576	22	**Comments:** See below proposed clarification. **Proposed change:** “It is considered appropriate to design the administration of the first dose in any cohort *of the single dose part* so that a single subject receives a single dose of the active IMP.”	Partly accepted. Text amended.
578	40	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Would it be worth mentioning here that these are referred to as sentinel subjects?	Text amended.
578	46	**Comments:** Suggest using the terminology "sentinel cohort" here as this is used in various published FIM documents.	Partly accepted. Text amended.
579	34	**Comment:** Please clarify what is meant by “adequate period of time”	Partly accepted. Text amended to include reference to uncertainty of the product.
579-581	9	**Comments:** Consider some more flexible language around use of sentinel. May be too much to do it in every study (may not be necessary) – must be a risk-based decision	Partly accepted. Text amended
579-581	51	**Comments:** The requisite time between dosing successive subjects within a cohort should focus on serious adverse reactions rather than any or all adverse events (this is made clearer in line 587). As such, we suggest adding language similar to that in line 587 to make this focus clear.	Partly accepted. Text amended.
579-582	32	**Comments:** The current text implies that after the sentinel subject, the remaining subjects in the cohort may be treated simultaneously. This is not endorsed in all cases. Depending on the risk associated with a given product and the subjects included in the CT, sequential dose administration in the remaining subjects of a cohort can be more appropriate **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		(..) adverse events. To mitigate the risk, further dose administration should be sequential within each cohort. Any non-sequential dose administration within a cohort should be justified. There should be an adequate period of time between the administration of treatment between the individual subjects in a cohort. The duration of the (…)	
579-589	16	**Comments:** This might be difficult to address, but what about defining expected review times and data formats (e.g., change from baseline) for safety variables to maintain safety? This would likely be difficult to address but thought I would bring up for discussion.	Partly accepted. Text amended.
581-582	47	**Comments:** The statement as written did not take into account the toxicology data that have been generated and focuses solely on PK and PD	Partly accepted. Text amended.
581-582	51	**Comments:** The statement as written did not take into account the toxicology data that have been generated and focuses solely on PK and PD.	Partly accepted. Text amended.
584	9	**Comments:** Does this refer to safety data only or does this include PK? We assume that PK might not always be necessary.	Partly accepted. Text amended.
584	47	**Comment 1:** The sentence should read: At the end of the observation period there should be a clearly defined review of all “predefined” data “by the investigator” before allowing dosing of further subjects in the cohort.The second half of the sentence (in the same manner as …) should be deleted.The decision to proceed with the next volunteers on the same dose level within a cohort should be specified and justified in the protocol including parameters, time and people. However, it is not necessary to apply the same rules as for the escalating to the next dose level for a complete cohort.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		For example, the inter individual variability of PK variables of the compound may not allow to make any decision based on data from one single volunteer only, thus it is not helpful after the first volunteer. Usually, PK data on a full dose cohort is necessary to allow any meaningful judgment on exposure levels/ PK variables and to allow reasonable comparisons to e.g. predicted exposures or previous dose cohorts. Therefore, the general requirement of PK data from single subjects is not considered justified. It may only be considered and senseful in specific cases (such as for compounds with high uncertainties in predictions of human exposure combined with steep dose-response curves concerning specific toxicities / adverse findings). The same may hold true for other parameters. Dependent on the factors as lined out in section 4 as well as in this section, the review of data may not need to follow the same rules such as the same composition of decision making groups or committees a review. For example, decision to start treatment of next subjects within a dose cohort may be taken by the investigating physician based on the predefined stopping rules for an individual HV laid down in the protocol. **Comment 2:** All data generated in a cohort may not be relevant. The dose escalation will only be performed when we have the relevant data, e.g. relating to exposure criteria or stopping rules. **Proposed change:** At the end of the observation period there should be a clearly defined review of all ~~relevant~~ predefined data before allowing dosing of further subjects in the cohort, in the same manner~~ as the precautions applied between cohorts (see section 8.2.7) and there should be dose stopping rules in place to prevent further dosing if any rule is met (see also section 8.2.10)~~. In the event of any serious adverse reaction, further administration of the IMP to subjects should be immediately stopped, so that further subjects in the cohort are not exposed.	
584-586	10	**Comments:** It is not clear whether only the data to be reviewed or also the decision making group needs to be the same for the decision to continue dosing after the first subjects of a cohort as for the decision to move to the next cohort. There should	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		be the option that the decision to continue within a cohort is taken by a defined but smaller expert group. In addition “all data” appears too general, the data should be relevant for decision making in an N=1 situation as after the first dose group of a dosing period. **Proposed change:** “At the end of the observation period, there should be a review of clearly defined data before allowing dosing of further subjects in the cohort, following similar precautions as applied between cohorts…”	
584-586	33	**Comments:** “all data” appears too general. **Proposed change:** “At the end of the observation period, there should be a review of clearly defined data before allowing dosing of further subjects in the cohort, following similar precautions as applied between cohorts…”	Partly accepted. Text amended.
584-586	47	**Comments:** A safety review within a cohort cannot be performed in the same manner as the review between cohorts for several reasons. First, the number of within-cohort subjects is significantly lower than the number of the whole cohort and may be as low as one if only one subject is exposed to IMP on the first day of a new dose level. To base decisions on a sample size as low as N=1 is usually not possible and in most instances not meaningful. Also the observation period of these within-cohort subjects is typically much shorter than for subjects between cohorts. These observation periods can be as short as 24h and may not be sufficient for obtaining a meaningful assessment of safety and tolerability nor are they sufficient to return the results of measurements such as PK. **Proposed change:** Delete “in the same manner as the precautions applied between cohorts”. Also no formal safety review should be	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		required, rather the absence of any trial-specific stopping rule should be considered as sufficient to continue dosing within the cohort.	
584-586	51	**Comments:** BIO suggests clarifying “review of all data”. **Proposed change:** At the end of the observation period there should be a clearly defined review of all data in the same manner as the precautions applied between cohorts (see section 8.2.7) before allowing dosing of further subjects in the cohort, ~~in the same manner as the precautions applied between cohorts~~.	Partly accepted. Text amended.
584-587	9	**Comments:** Does this mean a DV meeting within cohorts? And will this apply to all cohorts? Also in MAD? Is this approach realistic?	Partly accepted. Text amended.
584-587	15	**Comments:** Re: *Line 584-587: At the end of the observation period there should be a clearly defined review of all data before allowing dosing of further subjects in the cohort, in the same manner as the precautions applied between cohorts (see section 8.2.7) and there should be dose stopping rules in place to prevent further dosing if any rule is met (see also section 8.2.10).* – ‘*in the same manner as the precautions applied between cohorts (see section 8.2.7)*’ would require review of PK and PD data in addition to safety from the sentinel cohort; ‘*The review should include comparison of PK, PD or PK/PD data from any previous cohorts with known non-clinical data and safety information to inform the decision, as well as comparison to any initial or updated PK and/or PD modelling and simulation*’ as described in section 8.2.7. With only 1 active-treated subject, it will be very difficult to compare PK, PD, or PK/PD with existing data or to confirm the initial PK/PD modelling and simulation; results of such comparison/confirmation will be subject to unknown variability of this single active-treated subject PK and PD in the study population. We suggest to rephrase the highlighted phase in such a way that stopping rule	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		should be based on safety data.	
584-587	26	**Comments:** The text infers that data from sentinel subjects undergoes formal review before progressing to the rest of the cohort by the dose decision making group/committee ("…in the same manner as the precautions applied between cohorts…"). Whilst we agree that all data should be reviewed, this review is normally undertaken by the investigator, who is responsible for subject safety and who performs a review of all available source data, to enable a prompt and safe transition to the remaining subjects. ACRO recommends that clarification is included to allow the investigator to make the decision to proceed with dosing of the remainder of the cohort. **Proposed change:** After "(see also section 8.2.10)" insert the following sentences: "This review may be undertaken either by the investigator or by the dose decision making group/committee. The person or group responsible should be defined in the trial protocol."	Partly accepted. Text amended.
584-587	45	**Comments:** Suggest clarification, and reduction of sentence length. **Proposed change:** Suggest amend from: "At the end of the observation period there should be a clearly defined review of all data before allowing dosing of further subjects in the cohort, in the same manner as the precautions applied between cohorts (see section 8.2.7) and there should be dose stopping rules in place to prevent further dosing if any rule is met (see also section 8.2.10)." To: "At the end of the observation period there should be a clearly defined review of all data before allowing dosing of further	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		subjects in the cohort, **using similar precautions** applied between cohorts (see **also** section 8.2.7) **and with** stopping rules in place to prevent further dosing if any rule is met (see also section 8.2.10)."	
585	22	**Comments:** Does "in the same manner" mean a formal dose escalation committee decision? Can "all data" be defined more precisely? Would "all available data" be more appropriate wording? **Proposed change:** Please consider to change wording to make clear that the principal investigator needs to revise safety data only from the sentinel subjects within a defined timeframe.	Partly accepted. Text amended.
585	50	**Comments:** This sentence implies that all the clinical safety, vital signs, ECGs, and lab data are needed to expand the cohort after the two sentinel subjects are dosed. This will delay the progression of the study, and in some molecules clinical observation (e.g. without haematology, serum biochemistry and other safety labs) may be sufficient.	Partly accepted. Text amended.
587, 673	31	**Comments:** The evaluation of relatedness in serious adverse reactions (i.e. serious adverse event (AE) considered at least possibly related to the IMP administration) is not always transparent, correct or immediate. Therefore, it could be important for the safety of other study participants to stop dosing further study subjects until the SAE has been clarified. **Proposed change:** replace "serious adverse reaction" by "serious adverse events"	Partly accepted. Text amended.
587-	33	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
588		Recall the definition of a serious adverse reaction (as per line 673) **Proposed change:** (i.e. a serious adverse event (AE) considered at least possibly related to the IMP administration).	Text amended.
587-588	47	**Comments:** Text suggests that a single SAE would be a key stopping rule – this is appropriate for Healthy volunteer studies (as noted in section 8.2.10 stopping rules) if deemed potentially related to study drug, but may not be suitable for early patient studies where an AE could be disease progression. This should be clarified. **Proposed change:** In the event of any serious adverse reaction in a healthy volunteer study that is determined to be possibly IMP-related, further administration of the IMP to subjects should be immediately stopped, so that further subjects in the cohort are not exposed. Stopping rules for patient studies should be justified based on characteristics of disease progression. Once the nature of the SAE has been sufficiently characterised, and assuming data supports, the study may recommence either by: (i) if SAE determined not to be possibly IMP-related, dosing may recommence once that has been determined; (ii) if SAE is deemed possibly IMP-related, with the agreement of the CA via a substantial agreement. Once a stopping criteria is met, a substantial amendment would be required to re-initiate dosing at that dose level.	Partly accepted. Text amended.
587-589	20	**Comments:** Please clarify whether “subjects” in this instance refers to healthy volunteers, patients, or both. The text suggests that a single SAE would be a key stopping rule – this is appropriate for healthy volunteer studies (as noted in section 8.2.10 stopping rules) if deemed potentially related to study drug, but may not be suitable for early patient studies where an AE could be disease progression. Please confirm whether “serious” includes all seriousness criteria, or only events which are fatal/life-threatening for instance. Rationale for this request is based in the ANSM’s healthy volunteer safety considerations, which are very similar	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		in nature to this guideline but are limited to fatal events and those resulting in hospitalization experienced by healthy volunteers. **Proposed change:** In the event of any serious adverse reaction in a healthy volunteer study that is determined to be possibly IMP-related, further administration of the IMP to subjects should be immediately stopped, so that further subjects in the cohort are not exposed. Stopping rules for patient studies should be justified based on characteristics of disease progression. Once the nature of the SAE has been sufficiently characterized, and assuming data supports, the study may recommence either by: (i) if SAE determined not to be possibly IMP-related, dosing may recommence once that has been determined; (ii) if SAE is deemed possibly IMP-related, with the agreement of the CA via a substantial agreement. Once a stopping criteria is met, a substantial amendment would be required to re-initiate dosing at that dose level.	
587-589	39	**Comments:** Stopping the administration, the cohort and subsequently the study when a SAR occurs is a very important decision. We would like unambiguous clarification. **Proposed change:** In the event of any serious adverse reaction (i.e. a serious adverse event (AE) considered at least possibly related to the IMP administration), further administration of the IMP to subjects should be immediately stopped, so that further subjects in the cohort are not exposed.	Partly accepted. Text amended.
587-589	45	**Comments:** Stopping rule in sentence in line 587-589 appears to conflict in part with guidance in lines 672-676? Lines 587-589: “In the event of any serious adverse reaction, further administration of the IMP to subjects should be immediately	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		stopped, so that further subjects in the cohort are not exposed." Lines 672-676: "Stopping rules for healthy volunteer trials should include: • a 'serious' adverse reaction (AR) (i.e. a serious adverse event (AE) considered at least possibly related to the IMP administration) in one subject; • 'severe' non-serious ARs (i.e. severe non-serious AEs considered as, at least, possibly related to the IMP administration) in two subjects in the same cohort." **Proposed change:** Clarification needed.	
587-589	45	**Comments:** Stopping rule in sentence in line 587-589 may not always apply – for example with advanced therapy products (noted as out of scope of guideline – but if to be included this would be an area in need of clarification).	Partly accepted. Text amended.
587-589	47	**Comments:** In the event of any serious adverse reaction (related to administration of the IMP) the IMP should be stopped? Is there a consideration of expectedness? Meaning within a predefined range of expected SAEs administration might not to be stopped. DLT definition is usually related to the severity/toxicity of an adverse event but it is not necessarily related to seriousness. Stopping rules should be linked to dose limiting toxicity criteria defined in the protocol and if the upper limit is reached then IMP administration should be stopped. Currently this stopping rule is too general and would lead to trials being stopped unnecessarily. **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		"In the event of any serious unexpected adverse reaction defined in the DLT criteria and related to the IMP, further administration of the IMP to subjects should be immediately stopped, so that further subjects in the cohort are not exposed."	
587-589	47	**Comments:** "In the event of any serious adverse reaction, further administration of the IMP to subjects should be immediately stopped". For blinded, placebo-controlled FIH studies, the subject treatment assignment would need to be unblinded to confirm occurrence of the event on the IMP. In addition, when administering IMP for the treatment of life threatening illnesses without alternative treatment options, e.g. in oncology, the decision to stop administration of the IMP to subjects must be carefully considered in consultation with the study investigators and relevant health authorities. Stopping administration may not always be recommended and the edits below reflect this important consideration. **Proposed change:** In the event of any serious adverse reaction, further administration of the IMP to subjects should be immediately stopped, if the event is confirmed to have occurred on the IMP. In the event of a serious adverse reaction involving administration of IMP to patients with life threatening illnesses without alternative therapeutic options, the benefit: risk of further IMP administration needs to be carefully considered in consultation with the study investigators and relevant health authorities.	Partly accepted. Text amended.
590	22	**Comments:** What does "later stages of study design" mean? The wording is unclear and should be re-phrased. **Proposed change:** Consider to change wording.	Not accepted – examples given.
590	30	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		In the description of the precautions to apply between treating subjects within a cohort, the precautions are said to apply to Any (suggested above to become 'All') cohorts. However, this paragraph then says that the approach may also be appropriate later. This is moot since the precautions should apply to all cohorts. **Proposed change:** Delete the introduction of this paragraph and revise to: Care must be particularly taken in situations such as doses on the steep part of the dose response curve, when approaching target saturation levels or exposure margins to non-clinical NOAELs, in case of non-linear PK, or in light of emerging clinical signs or adverse events that do not meet stopping criteria.	Text amended.
590	32	**Comments:** It is not clear, what exactly is meant with "this approach". The sentinel dosing, the stopping rules? Please clarify	Partly accepted. Text amended.
590-592	47	**Comments:** The statement: "This approach may also be appropriate at later stages of study design …" seems to contradict the statement on line 575: "… first dose in any cohort …". As noted above, the sponsor suggests that sentinel should be recommended but not mandated in all circumstances, especially when proper justification for the non-use of sentinel subjects may be provided (eg. high level of precedence and known or benign pathway). sentinel cohorts are suggested in all cohorts of the single ascending dose study. **Proposed change:** From the comments above for lines 575-576, we believe the wording should be changed such that sentinel dosing is not necessary, and may be detrimental, (see Sentinel dosing comments above) for cohorts for IMPs of known or benign pathways.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
590-593	10	**Comments:** It is not clear what is meant by “at later stages of study design”. Staggering IMP administration in early dose escalation trials such as FIH is best practice and should not be limited to initial dose levels only. Statements made in lines 575-589 should refer to all stages that involve dose escalation parts in early clinical trials. **Proposed change:** Delete lines 590 – 593.	Not accepted – examples given.
590-593	16	**Comments:** I'm assuming "this approach" refers to the sentinel dosing and everything else covered in this section. If so I feel like this section could be edited to emphasize the situations where sentinel dosing may be appropriate.	Partly accepted. Text amended.
590-593	34	**Comments:** In healthy volunteers, a good understanding of the dose-response curve is often lacking during the early stages of the trial and drug development. This requirement may be difficult to implement in situations of high PK-PD variability and low sample size.	Partly accepted. Text amended.
590-593 & 617-618	3	**Comments:** The EMA Guidance is correct (lines 590-593) that more precautionary cohort-designs could be needed at later stages e.g. on the steep part of dose-response curve or when approaching target saturation levels or exposure margins. Conversely (lines 617-618), since the initial doses may be very low, early cohorts may not show any pharmacological effects.	Partly accepted. Text amended.
594	46	**Comments:** Should this section be more detailed with regard to who is contributing to data review? It is usual to have a Safety Review Committee in all the FIM studies: could this be considered as a formal recommendation?	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
594	51	**Comments:** For placebo control studies it should be specified whether the sponsor (or selected team members) could be unblinded for an efficient ongoing review of the results between cohorts and/or parts of the study.	Not accepted. Too specific detail.
594-624	20	**Comments:** To avoid misuse or misinterpretation of this guidance, it is important to clarify that PK data may not always be required between each dose escalation cohorts in all situations. As noted in line 612, the dose-exposure and exposure-response relationships are important to consider, and PK data from limited numbers of subjects from the initial few dose levels can sometimes mislead and misinform. It is important to make clear availability of PK data for dose escalation should be flexible based on the situation.	Partly accepted. Text amended.
595	30	**Comments:** PK and PD results from all previous cohorts must be available before starting the next cohort. Stating 'where available' offers the opportunity to say that they were not available. It is not required. **Proposed change:** Administration in the next cohort should not occur before participants in the previous cohort have been treated and the PK, PD and clinical data, including possible AEs, from those participants reviewed in accordance with the protocol.	Partly accepted. Text amended.
595-597	39	**Comments:** Not consistent with §8.2.9 line 644-646. We do prefer the flexible wording of those line, with the concept of "... minimum number of evaluable subjects required for review"	Partly accepted. Text amended.
595-597	41	**Comments:** The data to be reviewed between cohorts should include PK, PD and clinical data. The protocol should describe what data	Partly accepted. Text amended.

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		will be reviewed and this should be unambiguous with no option to review data only “if available”.	
595-597	47	**Comments:** The first sentence of the text is probably in line with the following: at very low doses PK results often are not available; in these cases it should be possible to combine PK results from the first cohorts, to make them available for assessment once an assessment would be feasible.	Partly accepted. Text amended.
595-598	22	**Comments:** Chapter 8.2.9. gives a definition of data needed for review between cohorts **Proposed change:** Suggest to create the link between the two chapter	Partly accepted. Text amended.
595-601	47	**Comments:** Data Set to review for Dose escalation – according to draft guideline we can still use earlier applied procedures by defining the appropriate “relevant” data set to review prior to dose escalation decision (Line 595-601). However at several places in the guidance they state “all data” to be reviewed (line 650 & others). Therefore, seems that the information is conflicting in the draft guidance.	Partly accepted. Text amended.
595-601	51	**Comments:** BIO notes this is the first mention of the duration over which safety data should be collected for use in the dose escalation decision. It would be useful to introduce this concept in Section 7.3 (dose escalation). It would also be good to note that for a biologic (*e.g.,* IgG mAb) the timeframes for collection of safety data should be longer than 48 hours. This is especially the case where an IgG mAb is administered subcutaneously and the serum Tmax may not occur until ~ 10 days post-dose.	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
595–606, 626–633	17	**Comments:** Consider that subjects may drop out or have significant protocol deviations, so a full dataset may not be available. **Proposed change:** Please cross-refer to section 8.2.9	Partly accepted. Text amended.
595–606, 683–688	47	PK-based (individual vs. mean) dose decisions, and requirements for dose escalation in general **Comments:** Using the non-clinical exposure (C_{max} or AUC) at the NOAEL to set dose stopping criteria may be too restrictive as discussed under topic 4. This issue, regardless whether or not the NOAEL is used as a stopping criterion, would be further exacerbated by limitations due to measurement and outlier (individual) PK assessment, rather than use of the mean for dosing decision making. There is certainly limited scientific rationale for comparing an extreme exposure in one individual in a cohort (i.e., an outlier value) to a safety margin derived from an average exposure value in the toxicology species. The therapeutic exposures in humans are typically not known for novel mechanisms, and cannot readily be predicted form non-clinical models. Therefore, exploration of safety in early phase studies (in preparation for later phase studies) should be allowed beyond non-clinical NOAELs when nonclinical toxicities beyond the NOAEL are considered monitorable, manageable, and reversible. Also, there is a risk that the PK dose stopping criteria could become unnecessary restrictive in cases: 1) Where NOAELs derived from the most sensitive species is based on an observed toxicity or exaggerated pharmacology, which can be scientifically justified as being irrelevant to the trial subjects or can be monitored in the FIH/early CT by an appropriate biomarker (e.g. weight loss of obesity compound). 2) Where NOAELs from longer repeated dose studies (13-, 26-, 39- week) are used for setting stopping criteria in SAD CTs. A totality of evidence approach to risk and subsequent monitoring in the FIH trials, taking all available data into	Partly accepted. Text amended including the addition of a new section on dosing.

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		consideration during the trial, is the most scientifically justified approach to dose escalation. 4. Safety data should be the primary driver to determine dose-escalation: a. There are many examples in which human are the most sensitive species for a given toxicity (including the French case), in which SAEs occurred within the NOAEL exposure range. b. There are also cases in which humans tolerate certain toxicity better than toxicity species, as a result, clinically beneficial doses has MOS < 1 (i.e. NSAIDS). c. PK should not be used as a surrogate for safety monitoring. 5. PK (exposure) data should be used to support phase 1 trials: a. In cases when the toxicity findings are not monitorable, irreversible and potentially life-threatening: in such cases, PK may be used for dose selection to safe guide safety of phase 1 subjects b. PK data can be used as supportive information for dose-escalation in most of cases in which tox findings are monitorable, reversible and non-life threatening. i. PK data from lower 2-3 doses can be used to predict the exposures at higher doses ii. Review of PK data may reveal supra-proportional exposure, in which cases increments of dose escalation should be decreased. 6. PD data, when available, may also aid the dose-escalation in phase 1 trials: a. Steep dose-response relationship may alert sponsors to reduce the increment of dose escalation, especially, the PD effect is of narrow therapeutic margin b. Increment of dose escalation may also decrease when E_{max} is approaching.	

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		Consequently we propose the following changes: **Line 597-598:** **Proposed change:** Thus all relevant data to the stopping criteria and to specific risks of concern from cohort “n” should be reviewed prior to allowing dosing of cohort “n+1”. **Lines 602-605:** **Proposed change:** All emerging PD, PK and safety data relevant to the stopping criteria and to specific risks of concern should be critically reviewed against the pre-defined stopping criteria (see section 8.2.10), including exposure limits that are not to be exceeded. (….) While there can be no delay for safety data, a lack of PD information or a reduced PK data set could be justifiable in some cases, such as a short duration of the PD effect, and in cases these data are not relevant to the stopping criteria and to specific risks of concern. **Lines 683-688** Proposed change: Deletion of the following~~: “Comparisons of the non-clinical and clinical exposure should be based on the maximum clinical exposure in an individual subject within a cohort and not mean (average) clinical exposure in a cohort.”~~ Suggest changing sentence to **"If severe toxicity or death are observed in a nonclinical species without premonitory signals, and no appropriate clinical biomarker is available, a dose stopping criterion should be included at the clinical exposure (Cmax or AUC) equivalent to the exposure achieved at the NOAEL determined in the most relevant non-clinical species in a study of relevant duration compared to the duration of the clinical trial. The NOAEL in this extreme case should be adjusted by safety factors if appropriate and**	

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		based on available PK data. Exploration of exposures beyond non-clinical NOAEL levels are justifiable if 1) toxicities are considered monitorable, manageable, and reversible - and 2) doses have scientific and medical justification ”	
595-624	47	**Comments:** The wording in this section is misleading that PK data from each current cohort may be required prior to dose escalation. **Proposed change:** This should be clearly advocated that PK analysis can be more robustly evaluated for potential nonlinearity and should be based on data from several dose levels. Specifically, PK data from the initial one or two dose levels are often of limited value and may even not be quantifiable. The value of PK data is once data are available at multiple dose levels. Sponsor should be able to justify an approach for PK data use in the protocol and CTA.	Partly accepted. Text amended.
596	10	**Comments:** The availability of PK data before drug administration in the next cohort can be ambiguous since it may refer to timely or biological availability. At lower doses, the consideration of PK data from the previous cohort may not be scientifically necessary. Thus a justification of PK data for cohort decisions should be introduced. **Proposed change:** “… and PK data, where justified, or possible AEs from those participants…”.	Partly accepted. Text amended.
596	22	**Comments:** PK data should always be available in an MAD study or MAD study part. **Proposed change:** Consider to change wording.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
596	47	**Comments:** Clinical: To avoid mis-use and abuse of this guidance, it is a need to clarify that PK data is not always required between each dose escalation cohort in all situations. As noted in line 612, the dose-exposure and exposure-response relationships are important to consider, and PK data from limited numbers of subjects from the initial first few dose levels can sometimes mislead and misinform. **Proposed change:** "where available" to "where appropriate" Sponsors should more explicitly describe rationale for PK sampling paradigm in protocol and the review of PK data.	Partly accepted. Text amended.
596-597	47	**Comment 1:** Availability of all PK data should not be the default prerequisite to escalate given that timing of sampling is driven by PK reasons (document elimination phase) rather than safety reasons; for drugs with a very long T1/2 the situation may be different but such situation should not drive the default process (BR). **Comment 2:** It is recommended that some flexibility is allowed (and described in the protocol) to make a decision to go to the next dose based on "incomplete" data (e.g. 1 subject's data missing for reasons not related to tolerability or safety).	Partly accepted. Text amended.
596-599	33	**Comments:** "all relevant data from cohort n" is too general. A minimum number of evaluable subjects required for review should be indicated in the protocol. Discrepancies with line 645 ("the protocol should clearly define the minimum number of evaluable subjects required for review").	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
597	9	**Comments:** Could relevant data distinguish between safety data (which are right immediate available) and PK data (which might be only available for 'n+2'; also for large molecules these criteria might be different)	Partly accepted. Text amended.
597-598	47	**Proposed change:** Thus all relevant data to the stopping criteria and to specific risks of concern from cohort "n" should be reviewed prior to allowing dosing of cohort "n+1".	Partly accepted. Text amended.
597-598	47	**Comments:** Sentence should read: Thus all relevant data "as defined in the protocol" from cohort n…. Reason: It should be clearly defined which data (including the observation period for these data) is the basis for this assessment. Refer to line 600 – 601. **Proposed change:** Thus all relevant data as defined in the protocol from cohort "n" should be reviewed prior to allowing dosing of cohort "n+1". Review of all previous cohorts' data in a cumulative manner is preferred.	Partly accepted. Text amended.
598-599	30	**Comments:** Recommend requiring review of all previous cohorts' data in a cumulative manner. **Proposed change:** All previous cohorts' data must be reviewed in a cumulative manner.	Partly accepted. Text amended.
602	25	**Comments:** The draft guidance mentions that PK-PD result from the most recent cohort must be available for dose-escalation decision. Will that be a strict requirement for all type of compounds? Even for biologics such as mAb? Please clarify if EMA	Partly accepted. Text amended.

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		considers there would be exceptions to that rule with appropriate justification.	
602	47	**Comments:** The statement implies that exposure limits must be defined in advance. If the nonclinical data suggest very large safety margins and that it is a relatively safe compound, it may not always be possible to provide an exposure limit, or the value provided may not be meaningful. Thus setting an exposure limit in such cases may in the end result in testing of clinical doses that have not fully assessed efficacious exposures.	Partly accepted. Text amended.
602-605	47	**Proposed change:** All emerging PD, PK and safety data relevant to the stopping criteria and to specific risks of concern should be critically reviewed against the pre-defined stopping criteria (see section 8.2.10), including exposure limits that are not to be exceeded. (….) While there can be no delay for safety data, a lack of PD information or a reduced PK data set could be justifiable in some cases, such as a short duration of the PD effect, and in cases these data are not relevant to the stopping criteria and to specific risks of concern.	Partly accepted. Text amended.
603	47	**Comments:** exposure limits may not always be imposed, e.g. if expected AEs are well monitorable, such limits may not apply. **Proposed change:** All emerging PD, PK and safety data should be critically reviewed against the pre-defined stopping criteria (see section 8.2.10), and if relevant should include exposure limits that are not to be exceeded.	Partly accepted. Text amended.
604-605	30	**Comments:** PD data is essential for understanding the novel human pharmacology of the medicine being tested. There should be no	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		reason for allowing it not to be analysed since it may change with dose. The protocol should clearly specify and justify what data will be reviewed. Multiple different PD tests might be done within a study; the protocol should specify that data from the most robust test will be used and that other PD tests are exploratory and won't be used for the decision. **Proposed change:** Delete: 'While there can be no delay for safety data, a lack of PD information or a reduced PK data set could be justifiable in some cases, such as a short duration of the PD effect.' Insert: 'The protocol should clearly specify and justify what PD data will be reviewed.'	
606	22	**Comments:** Definition of "short duration of PD" is unclear. e.g. hypoglycaemia can be short lasting but severe. **Proposed change:** Consider to change wording.	Accepted. Text amended.
606	26	**Comment:** To ensure clarity of decision making, ACRO recommends that the statement below should be added at the end of the paragraph. **Proposed change:** Add the following statement at the end of the paragraph: "All such justifications should be recorded in the trial master file."	Not accepted. Too specific detail.
607-609	28	**Comments:** The review should also include any consideration from an independent DSMB if applicable.	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed changes: The review should include comparison of PK, PD or PK/PD data from any previous cohorts with known non-clinical data and safety information to inform the decision, comparison to any initial or updated PK and/or PD modelling and simulation, as well as any consideration from an independent DSMB if applicable.	
607-616	47	**Comments:** PD marker is not always available for drugs with new mechanisms of action and especially for a FIH study in healthy subjects. In a case where a PK/PD model could eventually be setup before starting a FIH study, it is not easy to envisage the advantage of continuously updating a PK/PD or PD model using data from each cohort. If at all, this could be made more specific for drugs where the therapeutic margin is small or tolerability/safety is a known issue based on animal work. **Proposed change:** Wherever feasible, the review should include comparison of PK, PD or PK/PD data from any previous cohorts with known non-clinical data and safety information to inform the decision. The planned dose(s) should be adapted accordingly, if needed. In addition, the review should consider whether adaptation of the protocol in other areas is required to ensure continuing safety of trial participants, such as safety monitoring parameters and timings or length of the follow-up period. In specific situations where PK, PK/PD relationship are of limited value (e.g. signs of dissociation between PK and PD profiles and potential toxicities due to off-target effects at the administered human doses) dose escalation schemes and progression to further scheme) study parts need to be more cautious (e.g. consider a slower progression of the dose escalation scheme). **Additional comment:** While the reviewer agrees that a review of all available data taking different aspects into account (e.g. observed exposures, safety signals, PD effects, comparison with toxicology data) is absolutely necessary to critically assess moving to the next cohort, there are some aspects which should be considered: (i) For some indications there are no	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		(translatable) PD endpoints which can be assessed in short term trials/trials in healthy volunteers; (ii) even if PD endpoints exist the question is how to appropriately scale PD effects to humans for the proposed comparison and what the consequence of deviations between expected and observed responses have for the conduct of the study; (iii) especially in early clinical trials (SRD, MRD) the number of subjects per dose group provides limited information when it comes to identification and precision of parameter estimates of a model which is why one usually relies on the entirety of the data (or at least multiple dose groups) from such a trial to develop exploratory models for selected PK and PD endpoints. This is why the value and the robustness of conclusions drawn from model updates after each cohort is limited especially since the variability in PD endpoints can be expected to be high; (iii) logistical aspects of the bioanalytical measurements and the timelines of model development/ repeated update for PK/ PD models should be considered.	
612-616	51	**Comments:** BIO believes that this section may benefit from further clarification. In instances where there is dissociation between PK and PD, PK/PD models are of great use to first characterize in a mechanism-based way. If such models can be developed early on and validated from preclinical PK/PD, such tools are the most reliable way to model single dose human PD and use simulation to project multiple dose PK (hence select MAD doses in the most rational way). There may be cases where the disconnection is unexpected as it was not seen in preclinical species and thus cannot be adequately characterized as the underlying cause is not understood. As such, BIO suggests changing the text to signs of poorly characterized and/or unexpected dissociation. **Proposed change:** In specific situations where PK, PK/PD models are of limited value (e.g. poorly characterized and/or signs of dissociation between PK and PD profiles and potential toxicities due to off-target effects at the administered human doses) dose escalation schemes and progression to further study parts need to be more cautious (e.g. consider a slower progression of the dose escalation scheme).	Partly accepted. Text amended.
613-	22	**Comments:**	Accepted. Text

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
614		The example is confusing. **Proposed change:** Consider to delete.	amended.
617-618	32	**Comments:** The mere statements that initial doses may be very low and early cohorts may not show any pharmacological effect does not provide guidance. Thus, the consequence of this statement should also be included in the GL: “Where there is no response in a cohort the precautions for the next cohort should be the same as for the previous cohort. “ **Proposed change:** Unanticipated responses may require a revised dose escalation. Conversely, since the initial doses may be very low, it is anticipated that early cohorts may not show any pharmacological effects. Where there is no response in a cohort the precautions for the next cohort should be the same as for the previous cohort.	Partly accepted. Text amended.
619-620	20	**Comments:** Sponsors may not have access to IMP data of other sponsors unless it is published. **Proposed change:** “ …by data from comparable (investigational) medicinal products (if available to the sponsor).”	Partly accepted. Text amended.
619-620	33	**Comments:** Refers to SAD/MAD. The minimum time interval between cohorts should be stated in the protocol.	Partly accepted. Text amended.
619-623	18	**Comments:** We believe that the intent of this paragraph is to highlight the importance of ensuring that an appropriate minimum data	Partly accepted. Text amended.

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		set is obtained and minimum period of observation is completed, to facilitate appropriate decision making between cohorts. However, by referring to “time intervals” in the text, the reader could be mistaken into thinking that this is a comment about logistics (e.g. time taken for an assay to be completed). **Proposed change:** From Time intervals between cohorts should be guided by non-clinical and clinical PK and PD data and, if appropriate, by data from comparable (investigational) medicinal products. The time interval should be stated in the protocol. Flexibility to allow for a defined longer review time in the event of emerging data could be accepted, but shortening of the review time for any dose escalation should always require a substantial amendment. To The minimum data required between cohorts, for example duration of observation for adverse reactions and specific clinical, PK and PD parameters of importance, should be guided by non-clinical and clinical PK and PD data and, if appropriate, by data from comparable (investigational) medicinal products. The minimum data required should be stated in the protocol. Flexibility to allow for additional data in the event of emerging data could be accepted, but reducing the data required for any dose escalation should always require a substantial amendment.	
620	34	**Comments:** Health authorities have access to data regarding comparable competitor products that are not available publically, but are otherwise imperative to assess and consider. Please clarify how data from comparable products that are not in the public domain can/will be used in the evaluation of doses. **Proposed change:** Recommend removal or alteration of “from comparable (investigational) medicinal products.”	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
620	47	**Comments:** Sponsors to not have access to IMP data of other sponsors unless it is published. **Proposed change:** " …by data from comparable (investigational) medicinal products (if available to the sponsor)."	Partly accepted. Text amended.
620-621	21	**Comments:** The interval between cohorts is determined by data requirements from previous cohort(s) rather than time. **Proposed change:** To amend text as follows: **"**The ~~time interval~~ **minimum data requirements should be stated in the protocol."**	Not accepted. Reference is to timing.
621	9	**Comments:** Minimal time interval can be stated in the protocol; however it will finally depend on the operational logistics of scheduling DV meetings.	Not accepted. Too specific detail.
625	34	**Comments:** Consider including reference to the possibility of early switch from healthy volunteers to patients – please further discuss and clarify this approach in Section 8.2.8. Please also comment on the necessity of providing an interim report supporting the switch, perhaps via a substantial amendment.	Not accepted. Too specific detail.
625-636,	20	**Comments:** If dose selection and pre-defined criteria for safety and exposure are clearly described in the protocol, an interim report prior to the start of further dosing phases for studies with multiple parts are not needed.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "For studies with multiple parts….substantial amendment prior to the start of further dosing phases if there are changes to dose selection, design, or pre-defined criteria in the protocol"	
628	23	**Comments:** Typo: "initial" to be replaced by "initially" **Proposed change:** "The actual data need to be compared to the ~~**initial**~~ **initially** simulated expectations and refined in line with available clinical information."	Partly accepted. Text amended.
631	43	**Comments:** The section seems to apply to studies using a SAD/MAD design only. The applicability for the oncology setting using dose escalation followed by dose expansion should be clarified.	Not accepted. Too specific detail.
634	9	**Comments:** This will affect timelines of combined protocols. Interim DB locks will have to be implemented to create interim reports.	Partly accepted. Text amended (deleted).
634-635	9	**Comments:** Probably best to also ask for review of EC or is this included?	Not accepted. Text amended (deleted).
634-635	33	**Comments:** The content of the interim report to be submitted to the authorities (Central Authority and/or Ethics Committee ?) is unclear. Except in the cases of substantial changes in the protocol or unexpected results (e.g. in terms of safety or	Partly accepted. Text amended (deleted).

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		exposure), an amendment is not needed to proceed to the next part (see consistency with lines 495-496 and 503-509).	
634-636	3	**Comments:** The EMA Guidance suggests, but does not insist, see (lines 634-636) in Section 8.2.8 on Precautions to apply between study parts, that: “For studies with multiple parts, consideration may be given to submitting an interim report to the competent authorities for review as a substantial amendment prior to the start of further dosing phases”. Under which circumstances, properly dated and documented, might an interim report by unnecessary?	Partly accepted. Text amended (deleted).
634-636	14	**Comments:** The proposal to submit an interim report is unclear unless intended to accompany an amendment to the protocol. This creates uncertainty as to the expectations of this report. **Proposed change:** Suggest deleting.	Partly accepted. Text amended (deleted).
634-636	18	**Comments:** Unless emerging data from the clinical study negatively impact the risk:benefit assessment for a subsequent study part, or result in a requirement to substantially alter study conduct in a manner not already approved as part of an adaptive study protocol, there would be no changes to report and hence no need for an interim report or a substantial amendment. We propose this sentence is deleted. **Proposed change:** From For studies with multiple parts, consideration may be given to submitting an interim report to the competent authorities for review as a substantial amendment prior to the start of further dosing phases.	Partly accepted. Text amended (deleted).

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		To Delete the above paragraph	
634-636	21	**Comments:** If a trial runs as expected and within the boundaries set by an adaptive protocol and if there is no increase in risk and no approved toxicity/stopping rules have been met, it should not be necessary to submit “an interim report to the CA for review as substantial amendment prior to the start of further dosing parts.” This would cause delay and remove one of the main advantages (time savings) of running integrated protocols. **Proposed change:** We suggest deleting lines 634-636.	Partly accepted. Text amended (deleted).
634-636	22	**Comments:** If the interim safety data does not require a change in the protocol (i.e. where a substantial amendment is needed), it should not be required to submit interim safety data to the authority (“for read only”). **Proposed change:** Consider to change wording.	Partly accepted. Text amended (deleted).
634-636	24	**Comments:** the adoption of an Independent Data Monitoring Committee (IDMC) for the evaluation of the interim reports should be indicated	Not accepted. Too specific detail.
634-636	30	**Comments:** We are not sure of the point of this. If there are no issues and no need to change anything, why delay things by submitting an optional substantial amendment and waiting for a response? If there are issues or a wish to change	Partly accepted. Text amended (deleted).

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		anything, then the amendment is required. **Proposed change:** Delete lines 634-636	
634-636	39	**Comments:** In case no modification of the initial design, it should not be considered as a substantial amendment. The content of the interim report should be clarified **Proposed change:** For studies with multiple parts, consideration may be given to submitting an interim report (which may contain blind data) to the competent authorities for review as a substantial amendment prior to the start of further dosing phases, unless no changes in the pre-specified rules	Partly accepted. Text amended (deleted).
634-636	41	**Comments:** The suggestion that “For studies with multiple parts, consideration may be given to submitting an interim report to the competent authorities for review as a substantial amendment prior to the start of further dosing phases” should be recommended more strongly. Consideration should be given to placing the onus on the competent authority to request such measures where deemed appropriate.	Partly accepted. Text amended (deleted).
634-636	42	**Comments:** For studies with multiple parts, an interim report to the competent authorities before the start of further dosing phases appears to be an option (‘consideration may be given’) rather than a requirement. The guideline did not specify the circumstances under which an interim report should be prepared and submitted. **Proposed change:**	Partly accepted. Text amended (deleted).

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Specify for studies with multiple parts when an interim report is required to be submitted to competent authorities for review before the start of further dosing phases.	
634-636	43	**Comments:** In oncology studies this point is critical as the need to submit an amendment can delay access of patients to potentially lifesaving treatments. **Proposed change:** See general Novartis comment above	Partly accepted. Text amended (deleted).
634-636	47	**Comments:** If dose selection (or dose selection criteria) and pre-defined criteria for safety and exposure are clearly discussed in the protocol, an interim report prior to the start of further dosing phases for studies with multiple parts are not needed. **Proposed change:** “For studies with multiple parts….substantial amendment prior to the start of further dosing phases if there are changes to dose selection (or changes to the predefined dose-selection criteria), design, or pre-defined criteria in the protocol”	Partly accepted. Text amended (deleted).
634-636	47	**Comments:** If predefined safety criteria allow for further dosing- reporting to the competent authorities should not be required. Suggest revising accordingly **Proposed change:** For studies with multiple parts, consideration may be given to submitting an interim report to the competent authorities for review as a substantial amendment prior to the start of further dosing phases, unless predefined safety criteria allow for further dosing.	Partly accepted. Text amended (deleted).

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
634-636	49	**Comments:** The EMA Guidance suggests at lines 634-636 that: “For studies with multiple parts, consideration may be given to submitting an interim report to the competent authorities for review as a substantial amendment prior to the start of further dosing phases” (see lines 634-636) **Proposed change:** It is not clear whether it is the sponsor or the authorities who are making the substantial amendment. If interim reports are desirable we suggest that it should be clearly stated (a) that they are mandatory, and (b) precisely between which study parts they are needed, and (c) whether the later study parts need to wait on further approval.	Partly accepted. Text amended (deleted).
634-636	51	**Proposed change:** For studies with multiple parts, consideration may be given to submitting an interim report to the competent authorities for review as a substantial amendment prior to the start of further dosing phases. In case the results of a completed part are leading to a substantial change to the design in the subsequent part of the study, then a substantial amendment should be submitted for review prior to the next part. Otherwise, when interim results are provided for review without substantial change of subsequent design, we propose that these should be provided as a notification in parallel to the start of the next study part.	Partly accepted. Text amended (deleted).
635-636	46	**Comments:** If the review of interim report is a pre-requisite to continuation that is pre-specified up front, then it is not an amendment. What could be suggested in the Guidance is a process whereby the interim report would be communicated to the IRB. In practice this is often the case.	Partly accepted. Text amended (deleted).
637	46	**Comments:** The fact to have now new section 7.3 "Dose escalation" (with previous text included) and section 8.2.9 "Dose escalation	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		scheme" is a bit confusing, consider combining or cross referring.	
637	47	**Comments:** "Data collection from all subjects in a given dosing cohort should be complete to proceed to the next dose cohort". This sentence raises doubt about what is meant about "complete data collection" and for compounds with half-life of a week for data are collected for 5 times half-life, could lead to extensive delays in overall trial duration. The need for data collection before escalating the dose is more clearly described in section 8.2.7 line 595-599. **Proposed change:** Suggest rephrasing: "Relevant data collection (see 8.2.7) from all subjects in a given dosing cohort should be complete to proceed to the next dose cohort".	Partly accepted. Text amended.
637, 650, 651	8	**Comments:** 8.2.9. Dose escalation scheme All data (e.g. safety, PK and any other available information, such as PD) for the evaluable subjects should be considered for review **Proposed change:** 8.2.9. Dose escalation scheme All data (e.g. safety, PK and any other available information, such as PD) for the evaluable subjects should be considered for review (Annex 1 – template of Dose escalation scheme)	Partly accepted. Text amended.
638-651	24	**Comments:** the adoption of an Independent Data Monitoring Committee (IDMC) for the evaluation of the interim reports should be	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		indicated prior to allowing dose-escalation or the beginning of a new aprt of the study	detail.
638-651	30	**Comments:** Quality control of the data used for dose escalation needs to be considered. It is vitally important that the data being used for decision making are reliable and represent the source information. **Proposed change:** A statement should be inserted within this section emphasising the necessity for quality control of all data that are being used in the decision to escalate the dose.	Partly accepted. Text amended.
641	40	**Comments:** It states that evaluable subjects for the dose escalation are expected to have completed all study visits. This is not always the case, in particular for biopharms, where the follow up visit could be 3+ months after even just a single dose.	Partly accepted. Text amended.
641	47	**Comment 1:** “Evaluable’ subjects should be defined and it is expected that these subjects who have completed all planned study visits.” A FIH protocol, especially in oncology, could allow for subjects to continue taking the IMP for until disease progression or death. Thus, all planned study visits may span over months. Waiting for all subjects in a cohort to complete all planned study visits would impact overall study duration. **Comment 2:** This sentence should be amended: all planned study visits pre-specified as essential for the safety evaluation (see 643 below) **Proposed change:** Evaluable’ subjects should be defined and it is expected that these subjects have completed all planned study visits the	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		pre-defined observation period or have completed all planned study visits pre-specified as essential for the safety evaluation.	
641-642	17	**Comments:** This sentence is too vague. 'Evaluable' subjects must complete all planned study visits at which data required for the dose escalation is collected. They won't have completed all their planned study visits (eg their next treatment period or follow-up). **Proposed change:** Add after 'visits': needed to collect all the data required for the dose decision.	Partly accepted. Text amended.
641-642	21	**Comments:** Minimum data requirements in terms of "evaluable subjects" should specify the number of subjects from a cohort and the minimum data post-dose for each of these subjects that are required to be reviewed in order to make a decision to escalate or progress to another study part. The minimum data requirements post-dose should be determined by the pharmacokinetics and –dynamics of the IMP, to ensure that essential pharmacokinetic time points and safety/tolerability issues can be captured. It is usually not necessary that subjects "have completed all visits". For biologicals with a long half-life this could otherwise preclude progression of a trial for months. **Proposed change:** To amend text as follows: **"'**Evaluable' subjects should meet **minimum data requirements, i.e. have data collected and reviewed for a pre-specified time period post-dose".**	Partly accepted. Text amended.
641-642	33	**Comments:** The requirement that all planned trial visits have to be completed for a subject to be considered evaluable for dose	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		escalation decision is not applicable in early phases, especially regarding safety evaluation. **Proposed change:** Delete the requirement. Nevertheless, a definition of 'evaluable subjects' should be given in the protocol.	
641-642	47	**Comment 1:** Evaluable subjects should be defined and it is expected that these are subjects who have completed the visits predefined for the data review and safety assessment before further dose escalation. There may be compounds with long half-life where PK samples may be taken for weeks until they are completely eliminated. If the assessment can be made that the time of maximum drug concentrations (tmax) is passed, the drug concentrations are already substantially lower than tmax and the amount of data required for the review is qualifying for an adequate assessment and decision (e.g. follow up is only done to be able to completely assess PK parameters), it should be possible to start a new dosing cohort prior to the last visits, data samplings being taken. **Comment 2:** In oncology trials the treatment is in cycles. Dose escalation is usually after cycle 1 has been completed and not after all planned study visits have been completed. **Proposed change:** 'Evaluable' subjects should be defined and it is expected that these are subjects who have completed all planned study visits or subjects who have completed 1 treatment cycle in oncology trials.	Partly accepted. Text amended.
641-642	51	**Comments:** "Evaluable" subjects should be defined and it is expected that these are subjects who have completed all planned study visits. For an NCE, the subjects are most commonly domiciled for several days and all assessments are completed under on Visit. For biologics, there may be a period of confinement of several days but the healthy volunteers are subsequently	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		discharged. Subjects many then return for several visits in order to collect PK and PD samples. If a subject misses one such visit, there will still be adequate data to provide sufficient PK and PD data for the dose escalation decision. If PK and PD data are not part of the dose escalation decision then the statement as originally written is likely to be appropriate. Additionally, there will be study visits that occur after the last visit that provides data for the dose escalation decision. Therefore, the statement "all planned study visits" is inappropriate.	
641-643	20	**Comments:** The statements that "evaluable subjects... completed all study visits" and "data collection from all subjects … should be complete' appears to be at odds with the intent in other parts of the document. The Agency appears to support dose escalation based on pre-defined set of data whereas the two statements above would require ALL subjects at ALL time points to be complete. These requirements could be unnecessarily restrictive; for instance, in the case of a mAb, samples are usually collected for prolonged periods to characterize PK and potential ADA response but would not be overly important for a dose escalation decision. **Proposed change:** line 641 – "Evaluable subjects should be defined… who have completed all required study visits for dose escalation" Line 643 – "Data collection from all a pre-specified number of evaluable subjects in a given cohort should be completed to pre-specified time point to proceed to the next dose cohort".	Partly accepted. Text amended.
641-643	47	**Comments:** The statements that "evaluable subjects .. completed all study visits" and "data collection from all subjects … should be complete' appears to be at odds with the intent in other parts of the document. The Agency appears to support dose escalation based on pre-defined set of data whereas the two statements above would require ALL subjects at ALL timepoints to be complete. These requirements could be unnecessarily restrictive; for instance, in the case of a MAb, samples are usually collected for prolonged periods to characterize PK and potential ADA response but would not be	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		overly important for a dose escalation decision. **Proposed change:** line 641 – "Evaluable subjects should be defined… who have completed all required study visits for dose escalation" Line 643 – "Data collection from ~~all~~ a pre-specified number of evaluable subjects in a given cohort should be completed to pre-specified time point to proceed to the next dose cohort".	
641-644	10	**Comments:** The requirement that all planned trial visits have to be completed for a subject to be considered evaluable for dose escalation decisions is neither needed to ensure the safety of trial subjects nor will it in many instances be feasible. In order to ensure the safety of trial subjects, it is sufficient and well established standard practice to cover the period of highest risk / peak effect which has to be defined case-by-case based on the individual characteristics of the IMP (e.g. expected AE profile based on non-clinical data, expected PK and PD profile). In contrast, the timing of the last trial visit of a subject will focus on full characterisation of PK (e.g. 5-10 half-lives), PD and, if applicable, for biologics additional aspects such as ADA formation. Waiting for completion of all planned trial visits which in some instances may last for weeks and months is not reasonable / feasible. **Proposed change:** Delete the requirement, that all planned trial visits have to be completed for a subject to be considered evaluable. Instead allow the case-by-case definition of appropriate minimum requirements regarding observation period and data to be available in order to qualify a subject as evaluable.	Partly accepted. Text amended.
642	32	**Comments:** Please add the proposed text to further define the "evaluable" subjects. **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		(…) all planned study visits per protocol and without major protocol deviations.	
643	9	**Comments:** Again the word COHORT should be replaced (throughout the document) by DOSE LEVEL. If cohorts refer to a “dose level” this should be clearly defined	Partly accepted. Text amended.
643	17	**Comments:** The text refers to data collection from ‘all subjects’. However, provided that the minimum dataset is available (eg data from N subjects on active treatment up to N h after dosing), dose escalation should be allowed to proceed. The requirement for data to be ‘complete’ is too stringent. Data may still be evaluable, even if incomplete. **Proposed change:** Clarify that the minimum dataset must be defined for safety, PK and, if relevant, PD data. The definition must include the minimum number of subjects for whom data are available (eg 6 subjects, to ensure 4 subjects on active treatment), and the minimum time period (eg PK data up to 24 h after dosing). The definition should note that the evaluable subjects should have no significant protocol deviations, and any missing data points must not compromise interpretation of the results.	Partly accepted. Text amended.
643	47	**Comments:** This sentence should be reworded eg all predefined data, necessary for the safety evaluation, of all subjects in a given dosing cohort should be complete to proceed to the next dose. Reason: I) Exploratory biomarkers included in ECTs or other supportive markers are often not measured after each cohort but at the end of a study. II) Not all visits maybe included in safety evaluation, eg follow-up may be late after the last dosing and not necessary for a safety evaluation before dose escalation.	Partly accepted. Text amended.
643-	40	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
644		It is stated that data collection from all subjects in a given dosing cohort should be complete to proceed to the next dose cohort. However, this may not be practical for long acting molecules, whereby data may be collected for 6 months (or more) following single dosing.	Text amended.
643-644	51	**Comments:** The terminology “data collection” is unclear. This may include analysis of all samples collected. As such, we ask EMA to clarify what is meant by “data collection” as we believe additional specifics would be helpful.	Not accepted. Too specific detail.
643 - 644	53	**Comments:** The sentence “Data collection from all subjects in a given cohort should be completed to proceed to the next cohort” is too stringent. In practical terms, complete data collection would include the data collected at the end of study visit, as well as data which are collected for retrospective pooled analysis (eg genomics, etc), which might not be relevant in the short term to help deciding dose escalation. **Proposed change:** “**Collection of all relevant data** from all subjects in a given cohort should be completed to proceed to the next cohort”	Partly accepted. Text amended.
643-647	26	**Comments:** For oncology FIH studies it is sometimes the case that discussion on a regular basis regarding emerging adverse events and dose limiting toxicities between the investigator and the sponsor carries the greater weight in terms of decision making at the dose escalation/review meeting. ACRO therefore suggests that all relevant safety data need not be in the clinical database at the time of the dose escalation meeting. Data entered in the CRF should be supplemental to clinical discussion. This allows for a more expeditious review of the current dose, and we recommend that a statement is added to the guideline to acknowledge this. **Proposed change:**	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Add the following sentence at the end of the bullet point: “Clinical discussion/experience should also be a key factor in dose review and should be thoroughly documented.”	
647-648	53	**Comments:** Propose to add the following sentence: in the case where a given cohort does not have enough evaluable patients to review the data, the protocol should state that the slot of a non-evaluable patient might be replaced by another.	Not accepted. Too specific detail.
648	47	**Comments:** “Subjects who have discontinued for any reason should also be considered in the relevant component of data review.” Patients who discontinue before getting IMP due to any reason may not provide any meaningful data for dose escalation decision. **Proposed change:** Subjects who have discontinued for any reason after receiving at least one dose of IMP should also be considered in the relevant component of data review.	Accepted. Text amended.
648-649	9	**Comments:** Including reasons for discontinuation	Not accepted. Too specific detail.
650	10	**Comments:** The data review should include all data of the predefined parameters to be considered for review. Exploratory data which may be recorded during the trial may not be needed for the review. **Proposed change:** Change “All data” to “All predefined data”	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
650	30	**Comments:** PD data is required for safe FIH studies **Proposed change:** All data (e.g. safety, PK, PD, and any other available information) is required …	Partly accepted. Text amended.
650	32	**Comments:** With respect to safety all subjects treated should be evaluated, not only the evaluable subjects. Please modify text. **Proposed change:** All data (e.g. ~~safety~~, PK and any other available information, such as PD) for the evaluable subjects should be considered for review. With respect to safety, all subjects treated should be evaluated.	Partly accepted. Text amended.
650	40	**Comments:** Often all the data would not be reviewed, just key data such as AE's, PK, PD (in some instances, but this is often not the case as the data could be analysed in batch at the end of the study to reduce assay variability), key changes in lab parameters. There could be numerous other endpoints collected in the study that are not reviewed. **Proposed change:** "All data relevant for decision-making should be considered for review."	Partly accepted. Text amended.
650-651	21	**Comments:** It is often not feasible or necessary to review "all data" prior to making a decision to escalate or to progress to another study part. Some PD data may only be analysed at the end of a trial and is not essential for a safe progress of the trial.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		The protocol should clearly specify which data will be analysed and reviewed on an ongoing basis and used to make decisions. **Proposed change:** To amend text as follows: **"The protocol should clearly specify which** data (e.g. safety, PK and other available information, such as PD) for the evaluable subjects **will be analysed and reviewed on an ongoing basis and used to make decisions**."	
650-651	47	**Comment 1:** Change the sentence to read "All predefined data (e.g. safety …..)"Reason: Collection of data with coverage of Tmax and until the drug concentrations will be already substantially lower than tmax is considered acceptable. The amount of data required for the review to allow an adequate assessment and decision needs to be predefined and justified accordingly in the study protocol. Moreover it should be noted, that some data on biomarker may be collected optionally and/or are exploratory in nature and not required for the safety assessment. It should be possible to determine them at a later point in time, if this is pre-specified in the protocol. **Comment 2:** It is not always necessary to review PK data for studies post-FIH. If the FIH study provides sufficient PK data to predict multiple dose PK information and there is sufficient safety margin and benign toxicity profile, then review of further PK data in other studies may not provide information for decision making. **Proposed change:** **In FIH studies,** all data (e.g. safety, PK and any other available information, such as PD) for the evaluable subjects should be considered for review.	Partly accepted. Text amended.
650-	47	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
651		PK is not strictly required at each escalation especially if viewed as reasonable predictable, This should state "all available" data or "all relevant data". **Proposed change:** All available data (e.g. safety, PK and any other available information, such as PD) for the evaluable subjects should be considered for review.	Text amended.
652	47	**Comments:** Stopping for one related SAE may be appropriate for some programs, but not for others. Factors that may impact this are similar to those described for factors influencing the starting dose (i.e. novel mechanism, monitorability of risk, patient population, etc). **Proposed change:** We propose “Section 8.2.10 Stopping Rules” includes subheadings for “Dose Suspension” and “Dose or Study Termination” to help distinguish between the two sets of stopping criteria.	Not accepted. Too specific detail.
652-676	50	Stopping Rules for healthy volunteer trials **Comments:** We agree that the protocol should define clear and unambiguous stopping rules, and that such stopping rules serve as a protection for subjects in clinical trials. However, this recommendation, as currently written, is potentially overly stringent and does not leave room for medical judgment. The numbers of subjects with certain adverse reactions that would lead to stopping (i.e., line 676 “…two subjects in the same cohort”) appear somewhat arbitrary and would seem to encourage smaller size cohorts, which would minimize the chances of meeting stopping rules and would be at odds with the goals of phase I studies which are to better understand safety, tolerability, and PK. Also, if an SAE or severe non-serious AE occurred in a placebo-treated subject, even if considered possibly related by a blinded investigator, this should not trigger cessation of dose escalation. Thus, the text should clarify that these events need to occur in subjects who	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		have received the active drug. Published reports on phase I studies (e.g., BMJ 2015;350:h3271) have demonstrated that the majority of SAEs in healthy subjects are not drug related. If the Investigator and Sponsor agree after reviewing the data that the SAE is clearly not related to study drug (because a clear alternative explanation exists for the SAE), then stopping should not be necessary and a substantial amendment should not be required (as specified by lines 656-658). Furthermore, with regard to "severe non-serious ARs" severity may depend on the grading scale used, and it's important to note that there is no universally accepted grading scale, particularly for healthy volunteer studies. Also, there may be "severe" AEs that are not clinically significant, and clinical significance may in part depend upon the duration of the effect. Ultimately, there should be room for medical judgment in assessing clinical significance. **Proposed change:** Lines 653-656: "The protocol should define unambiguous stopping rules which result in an immediate stop to dosing. It should further be specified in the rule if it implies a final end of dosing or a possible temporary halt ~~with dosing re-starting after a full evaluation of available data and the approval of a substantial amendment.~~ ***In general, in FIH studies, all clinically significant adverse events should be presumed to be related to study drug, particularly in healthy volunteers. However, after further review of additional clinical data, the Sponsor and Investigator may conclude that one or more adverse events are not related to the study drug because an alternative and more-likely explanation has been clearly identified. If this occurs, the rationale for this decision must be clearly documented, and dosing may be re-started.*** ~~The submitted substantial amendment should include a justification of the proposed dosing for the continuation of the trial and details of any adjustments to the protocol including additional safety monitoring, if applicable."~~ Lines 672-676: "Stopping rules for healthy volunteer trials should include: • a 'serious' adverse reaction (AR) (i.e. a serious adverse event (AE) considered at least possibly related to the IMP	

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		administration) in one subject ***who received active study drug*** • 'severe' non-serious ARs (i.e. severe non-serious AEs considered as, at least, possibly related to the IMP administration) in two subjects in the same cohort ***if the severe effects are deemed to be medically significant by the Investigator or the Sponsor and occurred in participants who received active study drug"*** In addition, please state whether these stopping rules are applicable to a cohort of a specific size. Furthermore, please clarify if the severe AEs need to be in the same system-organ-class or should together suggest a pattern of toxicity.	
652-693	42	**Comments:** It should be emphasized in section 8.2.10 that changes to the stopping rules require the approval of a substantial amendment. **Proposed change:** Add: Changes to the stopping rules require the approval of a substantial amendment.	Partly accepted. Text amended.
653	22	**Comments:** How is "unambiguous" defined? **Proposed change:** Consider to replace "unambiguous" with "based on measurements"	Not accepted. Too specific detail.
653-656	14	**Comments:** It is not clear what is gained by specifying "in the rule if it implies a final end of dosing or a possible temporary halt with dosing re-starting after a full evaluation of available data and the approval of a substantial amendment." The recommendation is awkward since, at the time of writing the protocol, it will not be possible to know what type of factors	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		may lead to stopping the study. It should be entirely sufficient to specify that following triggering a stopping rule, a substantial amendment would be required to re-start dosing. **Proposed change:** "The protocol should define unambiguous stopping rules which result in an immediate stop to dosing. If a stopping criterion is met, a substantial amendment will be required to re-start dosing. ~~It should further be specified in the rule if it implies a final end of dosing or a possible temporary halt with dosing re-starting after a full evaluation of available data and the approval of a substantial 655 amendment.~~ The ~~submitted~~ substantial amendment should include a justification of the proposed dosing for the continuation of the trial and details of any adjustments to the protocol including additional safety monitoring, if applicable."	
654-656	10	**Comments:** A substantial amendment should not be needed for every case that dosing is re-started after a temporary hold, e.g. after full evaluation of an AE initially considered as an ADR. It should only be needed for the cases that constitute substantial changes to the pre-defined conditions of the protocol. **Proposed change:** "… after full evaluation of available data and the approval of a substantial amendment, <u>if applicable</u>."	Partly accepted. Text amended.
654-656	33	**Comments:** A substantial amendment should not be needed for every case that dosing is re-started after a temporary halt. It should only be needed for the cases that constitute substantial changes to the pre-defined conditions of the protocol. **Proposed change:** "… after full evaluation of available data and the approval of a substantial amendment, <u>if applicable</u>."	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
654-656	47	**Comments:** A substantial amendment should not be needed for any case that dosing is re-started after a temporary hold, e.g. after full evaluation of an AE initially considered as an ADR. It should only be needed for the cases that constitute substantial changes to the pre-defined conditions of the protocol. **Proposed change:** "… after full evaluation of available data and the approval of a substantial amendment, if applicable."	Partly accepted. Text amended.
655	47	**Comments:** Substantial amendment to what? If it is determined that dosing to the cohort can be restarted the only document for which an amendment may be needed or required is the ICD. In general, restarting after a safety event would likely require evidence that the event was not drug related since it would be assumed related until proven otherwise. **Proposed change:** Clarify what needs to be amended.	Partly accepted. Text amended.
656-658	46	**Comments:** it might be useful to retain the sentence for communications in case of multicentre trials (similarly to what is stated for communication of AEs in paragraph below) This revised Guidance seems to imply that any "temporary" halt would require a substantial amendment to resume the study as per protocol. Generally, in my experience, if there is a temporay halt it is often because of AEs that require further investigations/additional tests to confirm that they are not drug-related.	Not accepted. Too specific detail.
660	47	"Final stop to dosing and termination of the trial" **Comments:**	Not accepted. This may be in response to a

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Challenging to pre-defined termination of the trial in all scenarios. A substantial amendment could be more time efficient and cost effective to evaluate alternative approaches for safe use of IMP when compared to starting a new protocol. **Proposed change:** Final stop to dosing and termination of the trial or a possible temporary halt with dosing re-starting after a full evaluation of available data and the approval of a substantial amendment.	catastrophic event.
663-664	17	**Comments:** We don't understand what this means. **Proposed change:** Please clarify.	Accepted. Text amended.
663-664	22	**Comments:** - "First dosing period" is a confusing term. It should be made clear that it refers to sentinel sub cohort in the single dose part of the study - The wording "completed" should be revisited and instead reference made to "defined a minimum observation period" for the sub cohort. **Proposed change:** Please consider to change wording as stated in the comment.	Partly accepted. Text amended.
666-667	21	**Comments:** Please see previous comments on stopping/toxicity rules. "Progression to the consecutive parts of a trial" and "any dose escalation parts" would fit better under the term "toxicity" rules than under "stopping" rules. It is very rare that an entire trial has to be stopped. Usually progression/escalation is possible at dose levels/dosing regimens that may have a small	Not accepted. Need is for stopping rules.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		number of potential mild to moderate toxicities but do not meet stopping rules. **Proposed change:** To amend text as follows: **"Toxicity rules should be defined for** • progression of the next part of the trial • any dose escalation parts of the trial"	
671	30	**Comments:** Missing word – 'the' **Proposed change:** … outline decision points for the situation where stopping rules are met.	Accepted. Text amended.
672	9	**Comments:** HNV and early patient trials?	Not accepted. Too specific detail.
672	20	**Comments:** Please clarify if "Stopping" in this instance includes both temporary halting and final end of dosing, or only the latter. Please consider allowing sponsors to specify in which instances temporary halting may be more reasonable than final end of dosing, provided appropriate justifications are made in the protocol. It should be clarified that these stopping rules apply to active-treated subjects only (not placebo) with unblinding if required	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: line 672 – "Stopping rules for healthy volunteer trials, on active drug, should include:"	
672	33	**Comment:** also applicable to patients in early phase clinical trials.	Not accepted. Too specific detail.
672	53	**Comment and request:** quid for patients (i.e cancer patients)	Not accepted. Too specific detail.
672-676	21	**Comments:** The toxicities mentioned in these two bullet points would normally preclude further dosing within that dosing regimen, dose escalation and/or progression to new study parts at that exposure. They may (depending on IMP and study design) not stop the entire trial, e.g. the trial can continue at lower exposure dosing regimens. **Proposed change:** To amend text as follows: **"For healthy volunteer trials there should be clear rules in the CT protocol about the impact the following toxicities have on the continued dosing within a dosing regimen, dose escalation within a study part and progression to consecutive study parts:** • a 'serious' adverse reaction (AR) […] • 'severe' non-serious ARs […]"	Not accepted.
672-	23	**Comments:**	Not accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
676		A single serious AR (SAR) is considered too stringent to stop an entire first-in-human development program, in particular as a no-risk approach is applied in the causality assessment, especially in first-in-human studies. Two severe non-serious ARs is considered appropriate only if the regulator means two subjects presenting the same severe non-serious AR in the same cohort. **Proposed change:** "Stopping rules for healthy volunteer trials should include: • a 'serious' adverse reaction (AR) (i.e. a serious adverse event (AE) considered at least possibly related to the IMP administration) in ~~**one**~~ **two** subject**s**; • 'severe' non-serious ARs (i.e. **the same** severe non-serious AE~~**s**~~ considered as, at least, possibly related to the IMP administration) in two subjects in the same cohort."	
672-676	47	**Comments:** It should be clarified that these stopping rules apply to active-treated subjects only (not placebo) with unblinding if required. A serious AE or severe AE in a subject who received placebo should not be considered "at least possibly related" after unblinding, even if the initial investigator assessment was "related". **Proposed change:** line 672 – "Stopping rules for healthy volunteer trials, on active drug, should include:" We suggest that the guidance allows the stopping rules to be formulated in the protocol based on the compound's profile (instead of "one-size-fits-all" principle).	Not accepted. Too specific detail.
672-676	47	**Comments:** It should be specified that stopping rules apply in case of 'severe' non-serious ARs **of similar nature** in two subjects in	Not accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		the same cohort. **Proposed change:** Stopping rules for healthy volunteer trials should include: • a 'serious' adverse reaction (AR) (i.e. a serious adverse event (AE) considered at least possibly related to the IMP administration) in one subject; • 'severe' non-serious ARs (i.e. severe non-serious AEs considered as, at least, possibly related to the IMP administration) **of similar nature** in two subjects in the same cohort.	
672-680	52	**Comments:** Stopping rules for healthy volunteer trials are overly stringent for some healthy volunteer settings; where a better focus may be on rolling review of safety data. Some agencies may take this as mandatory stopping criteria for all studies. **Proposed change:** Stopping rules for healthy volunteer trials should ~~include:~~ ~~• a 'serious' adverse reaction (AR) (i.e. a serious adverse event (AE) considered at least possibly 674 related to the IMP administration) in one subject;~~ ~~• 'severe' non-serious ARs (i.e. severe non-serious AEs considered as, at least, possibly related to 676 the IMP administration) in two subjects in the same cohort.~~ give c~~C~~onsideration ~~should be given~~ to stopping criteria based on a rolling review of the data that takes account of 'moderate' non-serious ARs (i.e. moderate AEs at least possibly related to the IMP administration) and their relation to PD effects, the number of subjects in which they occur, concurrency of more than one within the same subject and potential safety signals identified for other	Not accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
672-693	28	**Comments:** The stopping rules are, in our opinion, too general. We would welcome more clarification as to the characteristic of the SAR and the type of data review that would then entail e.g. Infusion	Not accepted.
673-674	9	**Comments:** stopping rule for cohort? for dose escalation? for study? - suggestion to add Intermediate rule: temporary stop to investigate situation. - stopping rules also for patient trials?	Not accepted. Too specific detail.
673-676	13	**Comments:** Previously we commented “Causality assessment is particularly difficult by lack of clinical experience in this phase. Not previously described is actually an argument against causality. Please amend.” However, the text was not amended. We would like to refer to the guideline “ICH Topic E 2 A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting” the following is stated for an ADR: “a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out”. This means that the terminology Adverse Reaction already implies that the event is (possibly) related to the administration of the IMP. **Proposed change:** Please amend.	Not accepted. Terms used in line with ICH E2A.
673-676	47	**Comment:** The definition of ‘possibly related’ should be cross-referred to ICH E2A, Section A.1, page 7. **Proposed change:** Cross-refer to ICH E2A: “Possibly related means that there are facts (evidence) or arguments to suggest a causal	Partly accepted. Reference to ICH E2A added.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		relationship."	
673-676	51	**Comments:** The definition of 'possibly related' should be cross-referred to ICH E2A, Section A.1, page 7. **Proposed change:** Possibly related means that there are facts (evidence) or arguments to suggest a causal relationship.	Partly accepted. Reference to ICH E2A added.
675	17	**Comments:** To warrant stopping the trial, shouldn't the 2 severe adverse reactions be of a similar nature? **Proposed change:** 'severe, non-serious ARs **of a similar nature**…(i.e severe, non-serious AEs…'	Not accepted.
675	42	**Comments:** This sentence refers to 'severe' non-serious ARs **Proposed change:** 'severe' non-serious ARs should be defined within the guidance	Partly accepted. Reference to ICH E2A added.
675	47	**Comments:** There is no accepted definition of severe. The protocol should clearly stipulate what is meant by severe and how it will be categorized eg via CTCAE **Proposed change:** " 'severe' non-serious ARs (i.e. severe non-serious AEs, considered as, at least, possibly related to the IMP	Partly accepted. Reference to ICH E2A added.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		administration) in two subjects in the same cohort. The protocol should clearly stipulate what is meant by severe and how it will be categorized eg via CTCAE"	
675-676	3	**Comments:** Welcome is the extensive Section 8.2.10 on Stopping Rules but I suggest that the limitation "in the same cohort" (lines 675-676) may be overly restrictive when considering 'severe' non-serious adverse reactions (considered as, at least, possibly related to IMP administration) in two subjects in the same cohort.	Not accepted.
675-676	10	**Comments:** The stopping rule "Severe non serious ADRs in two subjects of the same cohort" only considers intensity of the adverse reaction but does not consider the cohort size. **Proposed change:** Change the respective stopping rule to "moderate or severe non-serious ARs in ≥50% of subjects in the same cohort"	Not accepted.
675-676	47	**Comments:** "Severe non serious ADRs in two subjects of the same cohort" are defined as stopping rule. This only considers intensity of the adverse reaction and does not consider the cohort size. **Proposed change:** Depending on the nature, intensity and duration of non-serious ADRs in at least 30% of the treated subjects, a stopping of dosing should be considered.	Not accepted.
675-681	27	**Comments:** We suggest that this language as written may be interpreted conservatively to halt dose escalation when a severe but clinically insignificant AR is observed in two patients in a cohort, and does not allow for application of clinical judgment.	Not accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		This concept may be more appropriately captured in a subsequent section. **Proposed change:** Stopping rules for healthy volunteer trials should include: • a 'serious' adverse reaction (AR) (i.e. a serious adverse event (AE) considered at least possibly related to the IMP administration) in one subject; Consideration should be given to stopping criteria based on a rolling review of the data that takes account of 'moderate' and 'severe' non-serious ARs (i.e. moderate AEs at least possibly related to the IMP administration) and their relation to PD effects, the number of subjects in which they occur, concurrency of more than one within the same subject and potential safety signals identified for other IMPs in the same class.	
677	25	**Comments:** Many non-specific ARs can meet a moderate severity during the course of a clinical trial (headache for instance). Involving the ARs of moderate severity in stopping criteria might halt a FIH clinical trial for non-specific ARs that are not safety signals. Please clarify if moderate ARs must be in relation to expected PD effects to be used as stopping criteria.	Not accepted.
677-678	42	**Comments:** This sentence discusses taking into account 'moderate' non-serious ARs **Proposed change:** 'moderate' non-serious ARs should be defined within the guidance	Partly accepted. Reference to ICH E2A added.
677-682	20	**Comments:** We assume that explicitly mentioning or alluding to a "rolling review" is the internal Sponsor's continuous assessment of emergent data. It is not expected that the internal assessment would be submitted to the CA (as a substantial	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		amendment), unless the Sponsor feels it is appropriate – notably, in the exceptional case that a pre-specification was not met. This should be clarified in the text: **Proposed change:** Consideration should be given to stopping criteria based on a rolling review continuous Sponsor assessment of emergent of the data that takes account of 'moderate' non-serious ARs (i.e. moderate AEs at least possibly related to the IMP administration) and their relation to PD effects, the number of subjects in which they occur, concurrency of more than one within the same subject and potential safety signals identified for other IMPs in the same class. In patients, changes from baseline measurements should also be considered, and not just absolute criteria based on upper limits of normal that might apply for healthy volunteers.	
677-682	47	**Comments:** It would be helpful to specify the nature of the "rolling" review of emerging safety data that may inform stopping rules while cohorts are currently ongoing; e.g. BLINDED review of individual subject-level data for pre-specified adverse reactions of "moderate" intensity (and/or UNBLINDED review by an independent safety medical monitor distinct from the study team). This is then distinct from the UNBLINDED review of aggregate safety data of a completed cohort and cumulative safety data for cohorts that completed so far at the time of a dose-level review meeting by the study team. **Proposed change:** "Consideration should be given to stopping criteria based on a rolling review of **individual subject-level or aggregate thesafety** data **that takes account offor** 'moderate' non-serious ARs (i.e. moderate AEs at least possibly related to the IMP administration) **in blinded or unblinded fashion while a cohort is currently ongoing or recently completed, respectively. This review may then also consider ARs** and their relation to PD effects, the number of subjects in which they occur, concurrency of more than one within the same subject and potential safety signals identified for other IMPs in the same class".	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
677-682	47	**Comments:** We assume that explicitly mentioning or alluding to a “rolling review” is the internal Sponsor’s continuous assessment of emergent data. It is not expected that the internal assessment would be submitted to the CA (as a substantial amendment), unless the Sponsor feels it is appropriate – notably, in the exceptional case that a pre-specification was not met. This should be clarified in the text: **Proposed change:** Consideration should be given to stopping criteria based on a ~~rolling review~~ continuous Sponsor assessment of emergent ~~of the~~ data that takes account of ‘moderate’ non-serious ARs (i.e. moderate AEs at least possibly related to the IMP administration) and their relation to PD effects, the number of subjects in which they occur, concurrency of more than one within the same subject and potential safety signals identified for other IMPs in the same class. In patients, changes from baseline measurements should also be considered, and not just absolute criteria based on upper limits of normal that might apply for healthy volunteers.	Not accepted. Too specific detail.
679	30	**Comments:** The relevance of the moderate AEs to the medicine’s target organ should be taken into account (e.g. the headaches in the Bial trial with a CNS-active medicine) **Proposed change:** and their relation to PD effects, the expected target organ (e.g. CNS), the number of subjects ….	Not accepted. Too specific detail.
681	22	**Comments:** What does “class” refer to? Chemical class? Mechanism of action? **Proposed change:**	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Please specify.	
681, 682	21	**Comments:** Changes from baseline should be considered in healthy volunteers also, not only in patients. A result outside the normal range may constitute a small or large change from baseline which is just as relevant for a healthy volunteer as it is for a patient when considering toxicities. **Proposed change:** To amend text as follows: ~~In patients,~~ Changes from baseline measurements should also be considered […]	Accepted. Text amended.
681-682	45	**Comments:** There is limited guidance on defining stopping rules for 'patients', compared to the guidance given in relation to 'healthy volunteers'. **Proposed change:** Further clarifications and examples would be welcome.	Not accepted. Too specific detail.
682	22	**Comments:** Consider to also add "lower" limits or more generally "outside normal ranges" as values below a threshold can also be pathological. **Proposed change:** Please delete "upper".	Partly accepted. Text amended
683	20	*"A dose stopping criterion of the clinical exposure equivalent to the exposure achieved at the NOAEL determined in the*	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		most sensitive non-clinical species should be included." **Comments:** Depending on the effect that is considered "adverse", there should be no requirement to have dose stopping criterion at this dose. The adverse effect may be "monitorable" and "treatable" and the doses administered up to that stage in the study will have given valuable experience to the sponsor to select the next appropriate dose.	Text amended.
683	22	**Comments:** See suggestion for change. **Proposed change:** "Clinical" to be replaced by "human". Consider stating rate (Cmax) and extent of exposure (AUC).	Not accepted. Too specific detail.
683	25	**Comments:** There is often a wide gap between NOAEL dose vs next dose at which an adverse effect was seen in animal models; this situation provides less accurate NOAEL and might limit the testing of supra-therapeutic dose(s).	Partly accepted. Text amended.
683-685	5	**Comments:** If the humans are less sensitive compared to the preclinical species, you can go higher than NOAEL.	Partly accepted. Text amended.
683-685	6	**Comments:** A dose stopping criterion based on human exposure not exceeding exposure at the most sensitive nonclinical NOAEL may not be appropriate for all cases, eg. if NOAEL-determining adverse effects are not severe, are reversible and monitorable clinically. Propose to soften wording according to ICH M3(R2) page 16: "*In the absence of adverse effects in the clinical trial, escalation above this AUC can be appropriate if the findings in the toxicity studies are anticipated to be monitorable,*	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		reversible, and of low severity in humans." **Proposed change:** A dose stopping criterion of the clinical exposure (Cmax or AUC) equivalent to the exposure achieved at the NOAEL determined in the most sensitive non-clinical species, adjusted by safety factors if appropriate and based on available PK data, should be included. In the absence of adverse effects in the clinical trial, escalation above this Cmax/AUC can be appropriate if the findings in the toxicity studies are anticipated to be monitorable, reversible, and of low severity in humans.	
683-685	10	**Comments:** The dose stopping criterion based on the clinical exposure equivalent to the exposure at NOAEL in the most-sensitive species practically limits the dose escalation to the safety factor applied for the MRSD if this is based on the PK approach with exposure equivalence at NO(A)EL. For a compound with a narrow therapeutic range, this criterion may preclude dosing to the therapeutic range even if there is no clinically detectable limitation of safety and tolerability. Under these circumstances, it may be required and reasonable to exceed NOAEL exposures in early clinical trials. Important aspects are among others relevance of non-clinical findings for humans as well as frequency, severity, monitorability and reversibility of these findings. **Proposed change:** Delete lines 683-685.	Partly accepted. Text amended.
683-685	13	**Comments:** It should be discussed if stopping criteria can be based on dose and whether this would apply to both enteral and parenteral administration. **Proposed change:**	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Please add discussion.	
683-685	14	**Comments:** This is an unfortunate addition; most FIH studies have been conducted with stopping rules allowing escalation beyond NOAEL exposures, and for good reasons. Stopping rules are typically defined to ensure stopping at the appropriate level based on safety and/or reaching some pre-defined pharmacodynamic readout (e.g. full inhibition of an enzyme). Reasons for escalating beyond the “expected human therapeutic dose range” include the need to fully explore safety and tolerability at higher dose, taking intra-subject variability, demographic factors, age, DDIs, organ impairment etc into account. In addition, full characterisation of the pharmacodynamic response may require escalating beyond NOAEL, safety and tolerability permitting. In addition, this requirement runs contrary to the concept of “supratherapeutic doses” in e.g. TQT studies. Dose levels are constantly varied in the subsequent clinical programme, and the need to increase dose based on emerging clinical data from patients is a common occurrence. A new rule requiring dose escalation to stop in the FIH trial because exposure has reached a value predicted from animal studies will not improve clinical safety; indeed, such a rule will likely require additional safety trials as clinical development progresses and more is learned about the product. The current text includes “unless scientifically justified”, which however reads as an exception. **Proposed change:** Suggest removing the strict requirement for a stopping rule based on NOAEL exposure and instead focus on stopping rules based on a weight-of-evidence approach, including emerging data from the FIH trial, animal safety data, animal pharmacology and mechanism of action of the product.	Partly accepted. Text amended.
683-685	20	**Comments:** The exposure metrics for stopping criteria should also include Cav, especially where the dosing interval in the tox studies was different to that intended in the clinic (eg for mAb, it is quite common to use QW dosing in the tox studies but Q2W	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		or Q4W in the clinic). **Proposed change:** "A dose stopping criterion of the clinical exposure (Cmax, AUC or equivalent to …"	
683-685	23	**Comments:** It is unclear how the dose stopping criterion of the clinical exposure equivalent to the exposure achieved at the NOAEL in the most sensitive non-clinical species needs to be interpreted in function of the exposure escalation rules outlined in ICH M3(R2), based on available toxicology data. **Proposed change:** "A dose stopping criterion of the clinical exposure (Cmax or AUC) equivalent to the exposure achieved at the NOAEL determined in the most sensitive non-clinical species, adjusted by safety factors if appropriate and based on available PK data, should be included. **For further guidance, please refer to ICH M3(R2)**"	Partly accepted. Text amended.
683-685	26	**Comments:** ACRO considers that the approach described in the draft guideline is overly prescriptive. An exposure cap based on exposure at the NOAEL is mostly unnecessary, e.g. if toxicity observed above the NOAEL is well monitored, transient, not serious and/or species dependent. An exposure cap is needed in the case of: 1) irreversible or severe toxicity, especially without a sentinel biomarker or 2) a risk of exceeding the exposure levels recorded in the general toxicity studies. ACRO also recommends adding a sentence to clarify that this stopping rule may imply a final end of dosing or a possible temporary halt with dose escalation resuming after a full evaluation of all clinical and preclinical data. **Proposed change:** The sentence should be revised to read: "……should be included in the case of: 1) irreversible or severe toxicity, especially without a sentinel biomarker or 2) a risk of exceeding the exposure levels recorded in the general toxicity studies. This	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		stopping rule may imply a final end of dosing or a possible temporary halt with dose escalation resuming after a full evaluation of all clinical and preclinical data."	
683-685	29	**Comments:** "A dose stopping criterion of the clinical exposure (Cmax and AUC) equivalent to the exposure achieved at the NOAEL determined in the most sensitive species, adjusted by safety factors if appropriate and based on available PK data, should be included." This is not always relevant in case of endogenous compounds or with compounds where systemic exposure does not predict safety (e.g. oligonucleotides). Hence deviations from use of clinical exposure as dose stopping criterion should be scientifically justified. Careful consideration should also be given to exposure to any significant metabolites in setting stopping criteria. **Proposed change:** "A dose stopping criterion of the clinical exposure (Cmax and AUC) equivalent to the exposure achieved at the NOAEL determined in the most sensitive species, adjusted by safety factors if appropriate and based on available PK data, should be included. Potential clinical risks should also be considered in selecting stopping criteria. This is particularly important in the case of any compound with which systemic exposure levels do not directly predict safety (e.g. oligonucleotides).Careful consideration should also be given to exposure to any significant metabolites in setting stopping criteria."	Partly accepted. Text amended.
683-685	30	**Comments:** In a SAD study, it may be perfectly reasonable to exceed the Cmax at the NOAEL if the pharmacological effects are directly related to it. AUC is usually more important to limit exposure in a MAD study. **Proposed change:** Delete current 683-685, and insert: Plasma concentrations corresponding to those at the NOAEL in the most sensitive	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		species provide a guide to stopping dose-escalation. While it may be reasonable to exceed the NOAEL Cmax in a single-dose escalation if no significant adverse events have been seen, organ toxicity on repeat dosing is usually more closely linked to the exposure in terms of AUC0-24 and it is generally unwise to exceed this.	
683-685	33	**Comments:** The dose stopping criterion based on the clinical exposure equivalent to the exposure at NOAEL in the most-sensitive species practically limits the dose escalation to the safety factor applied for the MRSD if this is based on the PK approach with exposure equivalence at NO(A)EL. This approach does not take into consideration the possibility to evaluate a supra-therapeutic range or even a therapeutic range beyond the NOAEL. It may be required and reasonable to exceed NOAEL exposures in early clinical trials. Important aspects are among others relevance of non-clinical findings to humans as well as frequency, severity, monitorability and reversibility of these findings. **Proposed change:** Delete lines 683-685.	Partly accepted. Text amended.
683-685	39	**Comments:** The proposal is too conservative and do not take into consideration the possibility to have a supra-therapeutic range or even a therapeutic range beyond the NOAEL. To go higher than the exposure associated with the NOAEL of most sensitive species should be allowed based on scientific rationale including all the data recorded in the current or past CT. In addition NOAEL definition is weak as based on the (1) subjective interpretation of finding as “no adverse” and (2) on the dose interval with the first toxic dose. It would be better to take into consideration the exposure associated with the first toxic dose (LOAEL) or even the highest non-severely toxic dose (HNSTD from ICH S9 guideline), and the characteristics of the toxicity observed i.e. reversibility and monitorability (Biomarkers). **Proposed change:** A dose stopping criterion of the clinical exposure (Cmax or AUC) equivalent to the exposure achieved at the NOAEL or the	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		LOAEL determined in the most sensitive non-clinical species, adjusted by safety factors if appropriate and based on available PK data, maybe be included.	
683-685	43	**Comment:** Such a dose stopping rule cannot be applied in the oncology setting. **Proposed change:** In healthy volunteer studies, a dose stopping criterion of the clinical exposure (Cmax or AUC)…	Not accepted. Too specific detail.
683-685	47	**Comments:** 'A dose stopping criterion of the clinical exposure (Cmax or AUC) equivalent to the exposure achieved at the NOAEL determined in the most sensitive non-clinical species, adjusted by safety factors if appropriate and based on available PK data, should be included.' We think that this is not applicable to all types of investigational products or therapy indications, depending on the severity, monitorability and treatability of the findings observed in the pre-clinical studies.	Partly accepted. Text amended.
683-685	48	**Comments:** The proposed stopping rule is based on PK exposure therefore indicating that PK data is required. There may be cases when the in-study PK data is not required or unavailable when considering the different approaches taken with biologics to PK assay and PK modelling based on preclinical data. **Proposed change:** A dose stopping criterion of the clinical exposure (C_{max} or AUC) equivalent to the **approximate** exposure achieved at the NOAEL determined in the most **relevant** ~~**sensitive**~~ non-clinical species, adjusted by safety factors if appropriate and based on available PK data, should **generally** be included. **Clear rationale must be provided in those instances where the data suggests the NOEL may be exceeded (e.g. High likelihood of species specific effect, with clear**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		premonitory signs and reversibility to permit monitoring and early stopping).	
683-688	47	**Proposed change:** Deletion of the following~~: "Comparisons of the non-clinical and clinical exposure should be based on the maximum clinical exposure in an individual subject within a cohort and not mean (average) clinical exposure in a cohort."~~ Suggest changing sentence to **"If severe toxicity or death are observed in a nonclinical species without premonitory signals, and no appropriate clinical biomarker is available, a dose stopping criterion should be included at the clinical exposure (Cmax or AUC) equivalent to the exposure achieved at the NOAEL determined in the most relevant non-clinical species in a study of relevant duration compared to the duration of the clinical trial. The NOAEL in this extreme case should be adjusted by safety factors if appropriate and based on available PK data. Exploration of exposures beyond non-clinical NOAEL levels are justifiable if 1) toxicities are considered monitorable, manageable, and reversible - and 2) doses have scientific and medical justification "**	Partly accepted. Text amended.
686-687	47	**Comments:** Stopping criteria using mean verses max exposure should be based on the identified pre-clinical findings and the type of toxicity observed. The mean exposure should be an appropriate parameter when combined with the totality of other data including emerging safety data. Mean exposure is used in the nonclinical data. **Proposed change:** Revise to indicate that individual clinical exposure should be considered and that if the maximum exposure is based on an unmonitorable nonclinical safety signal then dosing should be stopped if any individual subject exceeds that exposure.	Partly accepted. Text amended.
686-688	9	**Comments:** Although we certainly support the idea to look at individual exposure, this will result in unblinding.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
686-688	21	**Comments:** We suggest that both mean and individual maximum exposure limits tailored for the different parts of a trial should be given in a CT protocol. NOAEL is based on mean values and therefore it is appropriate to consider mean human exposures in relation to non-clinical mean exposures and to set limits accordingly. Individual exposure limits should be set in such way that the risk of experiencing clinically significant toxicity is minimised for each subject, taking into account PK variability of the IMP, the nature and reversibility of potential toxicities and how readily they can be detected and monitored. **Proposed change:** To amend text as follows: **"**Comparisons of the non-clinical and clinical exposure should be based on the **maximum mean (average) clinical exposure in a cohort and** on the maximum clinical exposure in an individual subject in a cohort."	Partly accepted. Text amended.
686-688	26	**Comments:** ACRO considers that the approach described in the draft guideline is overly prescriptive. Whilst the approach of limiting exposure based upon individual subjects is a prudent approach for some molecules, we would suggest that the guidance allow for use of mean data if scientifically justified. The draft guideline states that dosing would need to stop if an individual study subject has shown an AUC/Cmax above that associated with the NOAEL in the most sensitive animal species. However, the exposure measurements in the toxicity studies have outliers as well. Therefore, it should be judged on a case by case basis if outliers in exposure in a FIH study fall beyond the range observed in animals, and what the risk is, in view of the observed toxicity and exposure at higher dose cohorts in animals. ACRO recommends revising the current text.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Revise the sentence to read: “Comparisons of the non-clinical and clinical exposure should be based either on the maximum clinical exposure in an individual subject within a cohort or the mean (average) clinical exposure in a cohort, whichever is most appropriate to the molecule under study. The method used (with justification) should be defined in the trial protocol.”	
686-688	46	**Comments:** this is often debated in the Phase1 community: while the "individual" exposure approach makes sense for severe/non-monitorable toxicity (CNS tox/convulsion), less severe toxicity (GI tox) in animals could lead to a mean AUC cap	General agreement.
686-688	47	**Comments:** While apparently cautious, use of maximum PK exposures within a cohort would bias toward use of smaller size cohorts, to reduce the possibility of PK outliers. If a maximum PK parameter is used for comparison to non-clinical TK parameters, it would seem appropriate to compare with maximum non-clinical TK parameters (rather than mean no-clinical TK values). Also to be considered are the exposure projections at the next dose.	Not accepted. Too specific detail.
686-688	47	**Comments:** It is impossible to predict individual (95th percentile? extreme) data for individual subjects. Animal-based cut-off is also based on mean exposure value at NOAEL.	Partly accepted. Text amended.
686-688	47	**Comments:** On the use of maximum individual clinical exposure to be compared to the nonclinical toxicological exposure. Since NOAEL is reported as an average and included PK variability in the preclinical species, the sponsor notes that comparing individual exposure in the clinical cohort to the average in the nonclinical cohort is not a “like-to-like” comparison and should therefore not be recommended in most circumstances.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Remove this statement	
686-688	50	PK-based (individual vs. mean) dose decisions **Comments:** We recognize that basing decisions on exposure outliers (e.g., maximum rather than mean exposure) will provide an additional margin of safety, which could be appropriate when the potential toxicity is serious and when the dose-response relationship is steep. However, implementing this approach across all studies irrespective of the specific considerations will likely lead to inappropriate decisions. A blanket requirement (or "one size fits all" rule) to always use this approach is overly-stringent. Under current FIH study practice, outliers are already incorporated into dose escalation decisions, which are typically rendered based on the exposure, safety, and tolerability observed in all subjects. Strictly limiting dose escalation in all FIH studies based on outliers could lead to premature termination of dose escalation and could have the unintended consequence of preventing subsequent participants from achieving therapeutic exposures. This in turn could lead to erroneous conclusions about the activity or effectiveness of a drug. Please clarify the rationale for comparing an extreme exposure in one individual in a cohort (i.e., an outlier value) to a safety margin derived from an average exposure value in the toxicology species. Consider removing this requirement or providing clarification on the specific situations where such an approach is indicated. Proposed change: "~~Comparisons of the non-clinical and clinical exposure should be based on the maximum clinical exposure in an individual subject within a cohort and not mean (average) clinical exposure in a cohort.~~ ***In most cases, safety margins derived from nonclinical studies are based on a comparison of mean nonclinical exposures to mean clinical exposures. However, in certain circumstances in which the potential toxicity of the IMP is serious or***	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		unmonitorable and/or when the dose-response relationship is predicted to be steep, it may be appropriate to limit dose escalation based on individual rather than mean (average) exposure, i.e., when an individual achieves a certain exposure (e.g., some fraction of the NOAEL determined in the most sensitive non-clinical species).”	
686-688	51	**Comments:** BIO believes that this wording is very restrictive and has the potential to lead to study halt on the basis of an outlier. **Proposed change:** For an individual to be dose-escalated, comparisons of the non-clinical (average) and clinical exposure should be based on the ~~maximum~~ observed clinical exposure in ~~an~~ that individual subject within a cohort and not the mean (average) clinical exposure in ~~a~~ the cohort. For a new cohort to be dose-escalated, comparisons of the non-clinical (average) and clinical exposure should be based on the 90th percentile clinical exposure within the cohort and not mean (average) clinical exposure in that cohort. An alternative is also to calculate the probability to have subjects in the next cohort exceeding the exposure threshold.	Partly accepted. Text amended.
686-689	14	**Comments:** See previous comment regarding 683-685; this requirement is unfortunate and difficult to understand – even for a compound exhibiting moderate variability in exposure (e.g. %CV in the range of 25%), a single outlier would stop the study, even if no safety-, tolerability or PD-related criteria are met. In addition, and given the (welcome) emphasis on modelling approaches, the shift from a predicted group exposure at the next intended dose level to stopping rules based on a single individual defeats the purpose of model-based decision-making, effectively discouraging the use of models, which presumably was not the intention. **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Delete entire sentence.	
692-693	14	**Comments:** While agreeing with the principle of this paragraph, the wording appears too rigid – it may not be possible to formulate stopping rules for a novel compound with an unprecedented MoA for use in healthy volunteers. **Proposed change:** Additional stopping rules ~~should~~ **may** also be based on what is known about the PD of the drug (e.g. mode of action, chemical structure and others compounds in class or other classes).	Partly accepted. Text amended.
692-693	22	**Proposed change:** Please consider to delete examples in brackets (see general comment above)	Accepted. Text deleted.
692-693	26	**Comments:** ACRO considers that stopping criteria should not be only rule based and the study should also be stopped in case the investigator or sponsor decides that the risk to continue is not acceptable for the trial subjects. ACRO therefore recommends adding a statement to this effect. **Proposed change:** Add a statement to clarify that the study should also be stopped in any case in which the investigator or sponsor decides that the risk to continue is not acceptable for the trial subjects, and that the justification for this must be thoroughly documented.	Not accepted. Too vague for a guideline otherwise implicit.
692-693	30	**Comments:** The advice below is vague and not particularly helpful. Can this be made more explicit? 'Additional stopping rules should also be based on what is known about the PD of the drug (e.g. mode of action, chemical structure and others compounds	Accepted. Text deleted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		in class or other classes).'	
692-693	47	**Comments:** It is not clear how PD data that specifically relates to molecule concerned could inform additional stopping rules. The statement as such seems redundant and could be deleted without further clarification. It is also unclear as to how "chemical structure and others compounds in class or other classes" relates to the use of PD as a stopping rule. **Proposed change:** "~~**Additional stopping rules should also be based on what is known about the PD of the drug (e.g. mode of action, chemical structure and others compounds in class or other classes)**~~".	Accepted. Text deleted.
692-693	51	**Comments:** It is unclear as to how "chemical structure and others compounds in class or other classes" relates to the use of PD as a stopping rule. **Proposed change:** Additional stopping rules should also be based on what is known about the PD of the drug (e.g. mode of action, data from human or animal knockouts, regeneration of the target and others compounds that interact with the target in a similar manner ~~chemical structure and others compounds in class or other classes~~).	Partly accepted. Text amended.
693	6	**Comments:** "others compounds" - typographical error **Proposed change:** other compounds	Accepted. Text deleted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
695	9	**Comments:** Reference to all clinical staff but until this point no real reference to staff requirements (only described in section 8.4)	Not accepted. Too specific detail.
695	32	**Comments:** It is unclear, what is meant be “those reactions”. Is this a reference to some specific adverse reactions compared to “any other adverse events or reactions”? Please clarify.	Partly accepted. Text amended.
695	45	**Comments:** Suggested clarification **Proposed change:** Change from: “…to identify <u>those</u> reactions and how to respond to those or any other adverse events or reactions”, to: “….to identify **<u>any known</u>** reactions and how to respond to th**<u>e</u>**se or any other adverse events or reactions”.	
695-696	14	**Comments:** “All clinical staff should be trained to identify **those reactions** and how to respond to **those** or **any other** adverse events or reactions.“ As written, this phrase is incomprehensible…it is not clear what “those” refers to and apparently, there are then “other AEs” different from “those”. **Proposed change:** Clarify intent and reword.	Partly accepted. Text amended.
695-	26	**Comments:**	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
696		For clarity, ACRO recommends revising the statement to read as shown below. **Proposed change:** Revise the sentence to read: "All clinical staff who are in contact with study subjects should be trained to identify adverse reactions and how to respond to these or any other adverse events".	detail.
696	32	**Comments:** Please add “and direct” **Proposed change:** Rapid and direct access to the treatment allocation (…)	Not accepted. Too specific detail.
696	53	**Comments:** After adverse events or reactions….proposal to add the following sentence: “Special attention should be given to infusion related reactions. It is recommended to have a detailed set of instructions described in the protocol in case this might occur”	Not accepted. Too specific detail.
697-698, 720-722	21	**Comments:** Unblinding procedures in case of emergency are often described in a clinical pharmacology unit’s standard operating procedures which are inspected by the CA. In this case it should not be necessary to describe these procedures in every CT protocol. **Proposed change:** To amend text as follows: **For** double-blind **trial** designs **and in the absence of a description of the unblinding process in case of an emergency in an investigator’s standard operating procedures,** there should be clear instructions in the CT	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		protocol**."** We suggest deleting lines 720 to 722 as they repeat the above.	
697-680	3	**Comments:** Sound advice is given on the need for clear instructions in the protocol for unblinding in the case of an emergency (lines 697-680).	General agreement.
699	6	**Comments:** More clear guidance on the specific cases where counter measures to perceived risks need to be fully outlined (or not). **Proposed change :** Depending on the IMP and associated risk(s), the trial facility may be the adequate provider of 'supportive treatment emergency facilities'.	Partly accepted. Text amended.
699	24	**Comments:** A specific emergency management plan should be always prepared in advance for each protocol by a medical doctor expert in pharmacology and toxicology and shared with the emergency and intensive care staff of the facility.	Not accepted. Too specific detail.
699-700	26	**Comments:** As currently written, the guideline could be interpreted as requiring that treatment for all potential adverse events be defined in the protocol. This is unnecessary as most treatments will follow standard medical practice. ACRO therefore recommends replacing the phrase "certain type " with "significant". **Proposed change:** Replace "certain type " with "significant".	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
700-702	30	**Comments:** For staffing and supplies of antidotes, allow for the possibility that >1 subject may have the same AR in close proximity. This should include the availability of specific antidotes where they exist and a clear plan of availability of supportive treatment emergency facilities and medical staff to treat multiple patients.	Not accepted. Too specific detail.
702	53	**Comments:** Medical Staff **Proposed change:** experienced and trained medical staff	Partly accepted. Text amended.
703-704	42	**Comments:** This sentence states “The length of the monitoring period and the nature of monitoring within, and if deemed appropriate outside, the research site should be justified.” **Proposed change:** The guidance should provide direction on where they would expect to see documentation of this justification, e.g., within the protocol or a monitoring strategy/plan.	Partly accepted. Text amended.
705	32	**Comments:** In addition, “adverse events of special interest” should be defined and occurrence of these should also be communicated, as they could be indicative for toxicity. Please modify the text accordingly. **Proposed change:** Of high importance in the protocol is a prompt communication plan for SAEs, AEs of special interest, ~~and~~ suspected	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		unexpected serious adverse reactions (SUSARs) and/or serious safety-related protocol deviations between the sponsor, all study sites and investigators and trial subjects	
705	45	**Comments:** The sentence does not include reference to who is responsible for which parts of the communication, and could be made clearer. (For example the Sponsor would not communicate SUSARs to subjects/patients, nor would the subject/patients report any protocol deviation). We recommend the statement is broken down and clarified where activities are routine in a Clinical Trial and not specific to a FIH setting. **Proposed change:** Suggested change from: "Of high importance in the protocol is a prompt communication plan for SAEs and suspected unexpected serious adverse reactions (SUSARs) or serious safety-related protocol deviations between the sponsor, all study sites and investigators and trial subjects" To: "Of high importance is a communication plan in the protocol to ensure prompt safety reporting requirements for Clinical Trials are met, i.e. immediate communication of SAEs and serious safety-related protocol deviations from subjects/patients to study sites and to the Sponsor, and prompt onward communication of regulatory reports (7/15 days) of SUSARs by the sponsor to study sites and investigators."	Not accepted. Too specific detail.
705-707	47	**Comments:** "Prompt communication plan": should be revised to "plan for prompt communication" to enable action to be taken before further doses are given. It should also mention other emerging safety concerns or pre-defined events besides SAEs and SUSARs **Proposed change:**	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		"Of high importance in the protocol is a plan for prompt communication plan for SAEs and suspected unexpected serious adverse reactions (SUSARs) or serious safety-related protocol deviations, or other emerging safety concerns between the sponsor, all study sites and investigators and trial subjects, to enable action to be taken before further doses are given. It is particularly…"	
705-710	47	**Comments:** It should be clarified whether the same requirements apply to trials in healthy volunteers and in patients in whom SAEs occurrence is more frequent (e.g. oncology trials). This section may be gathered with lines 714-715, in order to clarify which event should be promptly communicated to which population (i.e. healthy volunteers / patients), and according to which communication rules.	Not accepted. Too specific detail.
707, 709-710	47	**Comments:** It should be made clear, that communication of adverse events of previous and/or ongoing cohorts to trial subjects is only deemed necessary when these adverse events are outside the expected potential adverse events as described in the Patient Information /Informed Consent and thus the benefit risk assessment is altered. The update of all affected clinical trial documents is then done via a substantial amendment.	Not accepted. Too specific detail.
711-713	8	**Comments:** Sponsors should ensure that processes are in place, before the trial starts, for expedited reporting of any SUSARs to the Member States concerned (MSC) (competent authority(ies)/ethics committee(s)), to the investigator(s) and to the EudraVigilance Clinical Trial Module. **Proposed change:** Sponsors should ensure that processes are in place, before the trial starts, for expedited reporting of any SUSARs to the Member States concerned (MSC) (competent authority(ies)/ethics committee(s)), to the investigator(s) and to the EudraVigilance Clinical Trial Module. In compliance with the Regulation (EU) No 536/2014, an informatic link will connect	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Eudravigilance system with the EU Portal and Database to share the main safety data related the CT.	
711-713	20	**Comments:** Please clarify what is meant by “expedited reporting”. There are already requirements for reporting procedures of SUSARS and for issues leading to temporary halt or premature termination of a trial. Guidance timelines from the point of time the Sponsor were made aware of a SUSAR should be stated.	Not accepted. Too specific detail.
711-713	47	**Comments:** Please clarify what is meant by “expedited reporting”. There are already requirements for reporting procedures of SUSARS and for issues leading to temporary halt or premature termination of a trial. Guidance timelines from the point of time the Sponsor were made aware of a SUSAR should be stated.	Not accepted. Too specific detail.
714	14	**Comments:** While agreeing with the principle of this addition to the guideline, the wording is too vague; “emerging safety issues” will need to be clarified to avoid over-reporting of e.g. headache or mild GI-disturbances (which are highly common in FIH studies, even in the placebo subjects). **Proposed change:** Consider qualifying “emerging safety issues” with “severe or serious”.	Not accepted. Too specific detail.
714	20	**Comments:** ‘Emerging safety issue’ should be better defined. Is this possibly an SAE/SUSAR?	Not accepted. Too specific detail.
714	53	**Comments:** “In case of emerging safety issues, investigators and participant (at any site) are to be informed as soon as possible”. I agree with the sentence and the recommendation, however, usually there is no documentation regarding the fact that	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		patients have been informed (unless there is an update of the ICF and requires the patients signature).	
714-715	22	**Proposed change:** In the case of emerging safety issues, investigators and participants (at any site) are to be informed as soon as possible, and at least prior to any planned next dosing ~~in multiple part or sentinel design.~~	Accepted. Text amended.
714-715	45	**Comments:** We suggest that the statement makes it clear where the responsibility of communication lies. **Proposed change:** Suggested change from: “In the case of emerging safety issues, investigators and participants (at any site) are to be informed as soon as possible” To: In the case of emerging safety issues, **the Sponsor should inform** investigators and participants (at any site) ~~are to be informed~~ as soon as possible	Not accepted. Too specific detail.
714-716	16	**Proposed change:** Define more concrete reporting timelines?	Not accepted. Too specific detail.
715	13	**Comments:** The term “sentinel”I was removed from all the previous sections. **Proposed change:** We propose to remove the term “sentinel” in this part as well for consistency.	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
715-716	20	**Comments:** Please clarify more precisely what is meant by “without undue delay”. The ANSM’s “Données de vigilance OBLIGATIONS DE DECLARATIONS IMMEDIATES DU PROMOTEUR” requires 24-hour notification for events which result in fatality or hospitalization in a healthy volunteer. While notification without delay in such an instance is inarguably best practice, 24-hour reporting presents significant operational challenges for study sponsors. Please also clarify if, in a single ICSR, such reporting would be in addition to regular SUSAR reporting or in place thereof. We propose further defining what is meant by “without undue delay,” also taking into consideration the operational challenges that would be presented by a requirement to notify MSC within 24 hours of awareness. “7-day safety report” should apply for unexpected SUSAR or life threatening adverse reaction reports.	Not accepted. Too specific detail.
715-716	39	**Comments:** Undue delay to be defined (e.g. within 48 hours) **Proposed change:** Any SUSAR in a healthy volunteer should be also reported to the MSC without undue delay (within 48 hours).	Not accepted. Too specific detail.
715-716	47	**Comments:** SUSARs reporting timelines are generally independently of whether the subject is a patient or healthy volunteer. Does the term “without undue delay” mean that SUSARs in healthy volunteers might require a different reporting timeline?	Not accepted. Too specific detail.
715-716	53	**Comments:** Vague wording (… participant to be informed…) **Proposed change:** Please provide clear expectation on the “information”. Amended Informed consent Form should be obtained. As a general comment : this guidance should provided more details on subject protection and information strategies for any protocol	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		change and safety profile modification	
716	22	**Comments:** What is meant by “undue delay”? There are clear PV time windows defined in the protocol. **Proposed change:** Consider to change wording.	Not accepted. Too specific detail.
716	32	**Comments:** It is not clear, why only SUSAR in HV should be reported to the MSC. Please delete “in a healthy volunteer”. **Proposed change:** SUSAR ~~in a healthy volunteer~~ should be also (…)	Not accepted. Too specific detail.
716	33	**Comments:** ‘undue delay’ is unclear.	Not accepted. Too specific detail.
718-719	30	**Comments:** It should be made clear that the investigator has the principal responsibility for patient safety and the sponsor for the overall integrity of the trial.	Not accepted. Too specific detail.
721-722	30	**Comments:** It should be made clearer that the decision to un-blind a study in an emergency rests with the Investigator. Line 721-722 does not place sufficient emphasis on this and should be made more explicit. **Proposed change:**	Not accepted. Too specific detail.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		It is also the case that unblinding in an emergency may be performed by the Investigator without involvement of the monitor or sponsor, where knowledge of the treatment received is needed for the immediate management of the subject. If unblinding is needed otherwise, the investigator should discuss with the sponsor, and the investigator has the right to withhold further dosing of the affected and other subjects whilst doing so.	
723-724	16	**Comments:** I interpret this to be a safety review or data monitoring committee.	Not accepted. Too specific detail.
723-727	3	**Comments:** Crucially, the EMA Guidance insists that – as for later phase trials - the composition of any decision making group or committee should be documented in the protocol so that their appropriateness (including independence) to participate in the monitoring and decision-making can be established.	Partly accepted. Text amended.
723-727	17	**Comments:** The text describes a safety monitoring committee, which is an approach taken in multicentre, late phase studies and is not appropriate for phase I trials. The group responsible for dose decisions should not be independent from IMP administration and monitoring and must include the investigator. The investigator is medically responsible for the safety of the volunteers and has witnessed any side effects – he or she must be part of the decision making process. **Proposed change:** Delete the last sentence of the paragraph.	Partly accepted. Text amended.
723-727	30	**Comments:** This should be a separate section entitled Trial steering group. Consideration should be given to specification of what expertise is required in a Trial Steering Group. For example, this could be related to the nature and action of the IMP or specific expertise in clinical pharmacology. This is particularly important in studies with integrated protocols or studies	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		which are being conducted at smaller research sites or where the sponsor is a small company with no in-house expertise. There should be an independent member of the TSC where possible. **8.4 Trial steering group** The composition of any decision-making group or committee should be documented in the protocol so that their appropriateness to participate in the monitoring and decision-making can be established. Other details to include are the exact remit of the group and the roles of all members in the committee or in relation to the sponsor. The members of the group should also be sufficiently independent from IMP administration and monitoring.	
723-727	36	**Comments:** It may be necessary to highlight the need to “integrate”/link data collected at FIH stage with that from future stages of trialling.	Partly accepted. Text amended.
723-727	42	**Comments:** The need for appropriate documentation of the decisions made by this group or committee was not addressed in the Guideline. **Proposed change:** It should be emphasized that written statements by this group must be available before progression to new dosing groups, for example.	Partly accepted. Text amended.
725-727	16	**Proposed change:** Add details of the decision making process and documentation of decisions made by the committee?	Partly accepted. Text amended.
725-727	40	**Comments:** Would it be useful to include details around whether the dose escalation review would be conducted in a blinded or	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		unblinded manner? This can vary from study to study. At least maybe mention that the blind status of the committee will be clearly documented. E.g. the meeting can be split into two. Open and closed portions, where the investigator often provides feedback on the safety of the subjects, and general observations in the open part. Then the closed part would exclude the investigator and unblinded data would be reviewed. Other studies may just have an open part, where only blinded data is reviewed; where the subject numbers for the PK profiles are not shared.	detail.
726	22	**Proposed change:** "…all members in the committee ~~or~~ *and* in relation to the sponsor."	Accepted. Text amended.
726-727	10	**Comments:** The requirement for independency of a decision making group should not exclude the participation of the investigator which may be implied by the current wording. The responsibility of the investigator for the trial subjects should be taken into account and considered for decision making in the trial. **Proposed change:** "The decision making group should also include members sufficiently independent from IMP administration and safety monitoring."	Partly accepted. Text amended.
726-727	21	**Comments:** The statement "The members of the group should also be sufficiently independent from IMP administration and monitoring" is difficult to understand. For FIH trials and consecutive early phase trials, the safety review committee (which makes decisions about trial progression) usually contains decision makers from the sponsor and investigator side, one of which is the Principal Investigator (PI) who carries the ultimate responsibility for the safety and wellbeing of their patients. The PK, PD and safety review is usually performed blinded. The PI is independent from monitoring as this is performed by an independent party on behalf of the sponsor. The PI is however closely involved in IMP administration and safety monitoring of subjects. The rationale why a PI should be independent from this in order to make decisions for	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		study progress is not clear. **Proposed change:** Please could you clarify or delete these lines?	
726-727	22	**Comments:** The Principal Investigator is a key member of decision making group and usually is involved in IMP administration and monitoring of safety. It is important that also representatives are members who have seen the reactions and have interacted with the subjects directly. **Proposed change:** Consider to change wording. “The members of the group *excepting the principal investigator or sub-investigator* should ~~also~~ be sufficiently independent from IMP administration and monitoring.”	Partly accepted. Text amended.
726-727	25	**Comments:** What is the exact meaning of: “*The members of the group should also be sufficiently independent from IMP administration and monitoring.*” We believe this sentence would avoid the participation of the principal investigator in the dose escalation decision. Investigator is directly involved in safety monitoring and surely needs to be part of any decision making group in early clinical trial. It makes sense to have external DATA SAFETY MONITORING BOARD in large trials involving multiple centers but not in single center FIH trials. **Proposed change:** Some member(s) of the group should be sufficiently independent from the IMP administration and safety monitoring, for instance an Independent medical expert(s).	Partly accepted. Text amended.
726-	26	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
727		The principal investigator is ultimately responsible for the safety of trial subjects at the site and therefore should be a member of the decision making group/committee. Consequently, ACRO recommends revising the statement to make this clear. **Proposed change:** Revise the statement to read: “The principal investigator should be a member of the decision making group/committee. Other members of the group should be sufficiently independent from IMP administration and monitoring".	Text amended.
726-727	29	**Comments:** “The members of the group (i.e., safety committee) should be sufficiently independent from the IMP administration and monitoring.” The Principal Investigator at the site has overall responsibility for IMP administration and subject monitoring. He is also the only one who has direct experience managing safety. Therefore, we consider it vital that the PI is part of the SRC. The safety committee should be quorate with the PI and at least two other appropriately qualified persons who are sufficiently independent of IMP administration and monitoring, and who are independent of the sponsor of the CT. **Proposed change:** “The members of the group (i.e., safety committee) should be sufficiently independent from the IMP administration and monitoring. The Principal Investigator is part of the safety committee. The safety committee should be quorate with the Principal Investigator and at least two other appropriately qualified persons who are sufficiently independent of IMP administration and monitoring, and who are independent of the sponsor of the CT.”	Partly accepted. Text amended.
726-727	30	**Comments:** The TSC and trial safety would benefit from limited independent membership, not directly associated with sponsor or study site. **Proposed change:**	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		The members of the group should also be sufficiently independent from IMP administration and monitoring. At least one of the members should be independent of sponsor and study site	
726-727	33	**Comments:** It should be required that the Investigator and the Sponsor's representative need to be implied in the decision making group. **Proposed change:** "The decision making group should also include members sufficiently independent from IMP administration and safety monitoring."	Partly accepted. Text amended.
726-727	39	**Comments:** In these very specific and highly specialized studies, the investigator as well as the sponsor should be part of the decision committee. This should be clarified as the current wording is ambiguous (… IMP administration and monitoring).We propose to remove the sentence, as the most important component of this § is on line 723-726 describing composition and processes. **Proposed change:** Remove the sentence 726-727	Partly accepted. Text amended.
726-727	41	**Comments:** The recommendations relating to the independence of decision making groups should be strengthened. Groups such as trial steering committees and data monitoring committees that are making decisions with potential safety implications should retain an element of independence from the sponsor organisation and any other organisation with a vested interest.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
726-727	47	**Comments:** The Principal investigator, as the ultimately responsible person, should always be involved in any relevant trial decisions such as dose escalation. However, per definition the PI is not independent from IMP administration and monitoring. **Proposed change:** Delete this statement.	Partly accepted. Text amended.
728	9	**Comments:** Recommend a EU-based accreditation (not local country accreditation) for identification of what is an “appropriate” site.	Not accepted. Too specific detail.
729-731	42	**Comments:** Additional detail underlined **Proposed change:** FIH/early CTs should take place in appropriate and qualified clinical facilities and be conducted by trained investigators who have acquired the necessary expertise and experience in conducting early phase trials and medical staff with appropriate level of training and previous experience of early phase trials. All study staff involved with carrying out study procedures should have documented protocol training.	Not accepted. Too specific detail.
732	22	**Comments:** Consider proposed change. These are not examples but necessary pre-requisites. **Proposed change:** Delete “as an example”	Accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
732-733	42	**Comments:** Investigators should also be trained in the trial protocol and procedures. **Proposed change:** They should also be trained on the trial protocol and procedures, and understand specific characteristics of the IMP, and of its target and mode of action.	Not accepted. Too specific detail.
734	5	**Comments:** Not all clinical trials are executed in hospitals, **Proposed change:** hospitalisation should be inpatient care	Accepted. Text amended.
734	37	**Comments:** We are in agreement with all points made with respect to investigator site facilities and staff experience and training. However, where a clinical research unit meets all criteria detailed (including an agreement and established transfer procedures with the nearby intensive care unit), we believe the need for the research unit to be hospital-based should not be an absolute requirement. We therefore and suggest that "(e.g. hospitalisation)" is either removed from line 734 or the wording is clarified to avoid any ambiguity for Competent Authorities/Sponsors/CROs as to the requirement for a unit to be hospital based. We also recommend that national accreditation schemes that have been established to ensure that CROs satisfy the requirements details in Section 8.4 (such as the MHRA Phase 1 Accreditation Scheme) are detailed and research units encouraged to volunteer/register where applicable.	Partly accepted. Text amended.
734	43	**Comments:** In oncology FIH studies patients are usually not hospitalised, unless available non-clinical and clinical data provide a	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		rationale to mandate it. **Proposed change:** “FIH/early CTs should take place under controlled conditions (e.g. including hospitalisation if considered appropriate),…”	
734-735	26	**Comments:** It is not necessary for FIH/early clinical trials to be performed in a hospital setting, as long as appropriate emergency facilities and arrangements are in place. Consequently, ACRO recommends revision of the sentence in order to clarify this. **Proposed change:** Revise the sentence to read: "FIH/early CTs should take place under controlled conditions in appropriate facilities (e.g. on a hospital campus or within 10 minutes of a hospital with intensive care facilities to facilitate rapid emergency transfer if needed), with the possibility of close supervision of study subjects during and after dosing as required by the protocol."	Partly accepted. Text amended.
737	24	**Comments:** FIH protocols implementation should be limited to the facilities where an emergency and intensive care unit is available	Partly accepted. Text amended.
738-740	6	**Comments:** Clear differentiation to the type of risk IMPs might or might not have could be stressed when requiring establishment of contacts between clinical sites and ICUs. The risks posed by some IMPs may be adequately handled at the trial site. **Proposed change:** Pertinent to the risks of the IMP, procedures should be established …	Not accepted. Too specific detail.
738-740	26	**Comments:** ACRO recommends that this is sufficiently important that the guideline should clarify specific responsibilities to be	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		defined, as indicated in the proposed change below. Additionally, trial subjects who experience a serious adverse event may be admitted initially to a hospital department other than the intensive care unit for evaluation and/or treatment. Consequently, the text here should not refer specifically to the intensive care unit (ACRO's proposal on lines 734 – 735 above refers to the need for the hospital to have intensive care facilities). **Proposed change:** Revise the sentence to read as follows: "...regarding the responsibilities and undertakings of each in the transfer and care of patients, and communication of relevant IMP specific information to the hospital and timely communication on clinical findings, which are relevant for other study subjects, from the hospital to the clinical pharmacology unit."	detail.
738-740	29	**Comments:** "Procedures should be established between the clinical research unit and its nearby intensive care unit regarding the responsibilities and undertakings of each in the transfer and care of patients." This counsel of perfection should perhaps acknowledge the realities of emergency healthcare provision in different states. Once an acutely ill subject is transferred to the care of the ambulance service in the UK (for example) it is not possible for the research unit to dictate what facility they will transfer the subject to. **Proposed change:** "Procedures should be established between the clinical research unit and its nearby **preferred** intensive care unit regarding the responsibilities and undertakings of each in the transfer and care of patients. **Especially where transfer to the preferred intensive care unit is not possible then the clinical research unit should do whatever is possible to optimise referral including accompanying the subject when possible and providing details of the study as well as study physician contact details to the receiving physician as clinically indicated."**	Not accepted. Too specific detail.
738-740	53	**Comments:** Procedures and responsibilities with a nearby ICU should not only consider transfer and care. Medical Charts of the ICU	Not accepted. Too specific

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		should be immediately accessible to relevant Clinical Trial Staff. This may not be the case with ICU staff not familiar with clinical trials even trained to the protocol & the IMP. **Proposed change:** Contractual obligations with ICU should clearly established that there is no restriction to trial personnel to access the patient Med Chart	detail.
739	22	**Comments:** Nearby refers to distance, time to reach intensive care is more relevant. **Proposed change:** "Procedures should be established between the clinical research unit and ~~its nearby~~ *the* intensive care unit regarding the responsibilities and undertakings of each in the transfer and care of patients"	Not accepted. Too specific detail.
740-742	30	**Comments:** Whilst FIH / early CTs in healthy volunteers are frequently conducted at a single site, it is important to emphasise that this may not be possible for FIH / early CTs in patient groups. In addition, whilst single site options are advantageous in gaining 'collective experience', it is important to note that when multiple sites are being used there should be adequate procedures in place to share information between sites and that this would not necessarily materially affect the safety or risk of multiple site studies.	Partly accepted. Text amended.
740-742	47	**Comments:** It would be difficult to conduct FIH/early CTs for IMP at a single site if these studies were conducted in patients. Patient recruitment for these studies would be difficult for a single site especially for rare and uncommon disease. This should not require a justification by default.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "All FIH/early CTs for an IMP should preferably be conducted at a single site (to gather collective experience). Studies in patients may require several sites in order to enrol a sufficient number of patients in a reasonable timeframe. When different sites are involved for other reasons, this should be justified."	
740-742	47	**Comments:** The two last sentences should be deleted. Reason: There is no value in adding this sentence to the guideline. In section 8.2.11. line 707 to 710 consideration wrt communication in case of multicenter studies are given. Therefore, an emphasis on single site study at the end of the guideline is inconsistent.	Partly accepted. Text amended.
740-742	51	**Comments:** For studies in healthy volunteers, it is feasible to conduct studies at a single site. However, for studies in patients it may not be feasible to conduct the study at a single site in a reasonable timeframe due to the scarcity of the patients.	Partly accepted. Text amended.
741-742	20	**Comments:** It would be difficult to conduct FIH/early CTs for IMP at a single site if these studies were conducted in patients. Patient recruitment for these studies would be difficult for a single site especially for rare and uncommon disease. Please also clarify where in the CTA would the justification for multi-site FIH occur?	Partly accepted. Text amended.
741-742	26	**Comments:** ACRO recognizes that the need for an appropriate communication plan between multiple sites involved in a trial is referenced in lines 705 – 710. However, ACRO believes that this is such an important issue with regard to subject safety in FIH trials in healthy volunteers that it should be reiterated here. However, use of multiple sites for patient FIH studies (such as oncology) is standard practice. Additionally, use of multiple sites is also standard for umbrella protocols including both healthy volunteers and patients. ACRO therefore proposes the following revision.	Partly accepted. Text amended.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Amend the sentence to read: “All FIH trials (or parts thereof) in healthy volunteers for an IMP should preferably be conducted at a single site (to gather collective experience). When different sites are involved in a FIH healthy volunteer study, this should be justified and a communication plan established for communication of safety data or rapid implementation of corrective or preventive actions at all study sites and investigators.”	
741-742	29	**Comments:** “All FIH/early CTs for an IMP should preferably be conducted at a single site (to gather collective experience). When different sites are involved, this should be justified.” If this is not feasible, for example in patient studies where multiple sites are usually required for enrolment, consideration should be given to the management of any extra risks that might arise from the use of multiple sites. **Proposed change:** “All FIH/early CTs for an IMP should preferably be conducted at a single site (to gather collective experience). When different sites are involved, this should be justified. If different sites must be involved, for example in patient studies where multiple sites are often required for enrolment, the protocol should include appropriate measures to reduce any extra risks that might arise from the use of multiple sites.”	Partly accepted. Text amended.
741-742	42	**Comments:** This sentence states “When different sites are involved, this should be justified.” **Proposed change:** The guidance should provide direction on where they would expect to see documentation of this justification, e.g., within the protocol.	Partly accepted. Text amended.
741-	47	**Comments:**	Partly accepted.

Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
742		It would be difficult to conduct FIH/early CTs for IMP at a single site if these studies were conducted in patients. Patient recruitment for these studies would be difficult for a single site especially for rare and uncommon disease. This should not require a justification by default. **Proposed change:** "All FIH/early CTs for an IMP should preferably be conducted at a single site (to gather collective experience). Studies in patients may require several sites in order to enrol a sufficient number of patients in a reasonable timeframe. When different sites are involved for other reasons, this should be justified."	Text amended.
741-742	53	"Preferably be conducted at a single site". This particular recommendation is not listed in the "Evaluation of anticancer medicinal products in man (CPMP/EWA/205/95 Rev 4)". **Proposed change:** Clarify that this might not be applicable in oncology studies.	Partly accepted. Text amended.
742	9	**Comments:** Early CT's include early patient trials as well? These are most of the times multicentre studies.	Partly accepted. Text amended.
742	28	**Proposed change:** We would welcome some clarification as what type of clarification would be acceptable to have more than 1 site for a FiH. For example, are recruitment difficulties or logistic issues acceptable reasons? We also think that in case of having multiple sites, clear routes of communication must be established to ensure the safety of the subjects.	Partly accepted. Text amended.