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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Overview of comments on 'Concept paper on the revision of the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products' (EMA/CHMP/446302/2016)

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that commented on the draft document as released for consultation (*note four parties requested their comments not to be published*).

Stakeholder no.	Name of organisation or individual
2	National Coordinating Center of Clinical Trials in Cuba
3	Medicines Assessment Ltd
4	Dr Mary Haines, consultant for the NSW Ministry of Health in Australia on a Framework for early phase clinical trials
5	Duke University Medical Center and Associate Director, Duke Clinical Research Unit.
6	NCD Pharmacology, Shire
7	Anna Maria Lepore
8	eResearchTechnology, Inc.
9	Hammersmith Medicines Research Ltd
10	ACRO (Association of Clinical Research Organizations)
11	Joachim Boos, Prof. f. exp.päd.Onkologie, Klinik und Poliklinik für Pädiatrische Hämatologie und Onkologie, Münster
12	Edinburgh Phase I / First in Human Study Review Committee (PISRC)
13	International Plasma Fractionation Association (IPFA)
14	PAREXEL International
15	Quotient Clinical Limited



Stakeholder no.	Name of organisation or individual
16	German Pharmaceutical Industry Association (BPI e.V.)
18	International Consortium for Innovation and Quality in Pharmaceutical Development (IQ)
20	EUFEMED – European Federation for Exploratory Medicines Development
21	Quintiles Medical and Scientific Safety Review Group
22	Christian Funck-Brentano M.D., Ph.D., FESC, Professor of Medicine and Pharmacology, Univ Pierre & Marie Curie - School of Medicine, FRANCE
23	European CRO Federation (EUCROF)
24	Health Research Authority (HRA)
25	EFPIA
26	REGenableMED consortium
27	Novartis Pharma AG
28	Club Phase I, Paris, France
29	Royal College of Physicians (RCP)
30	Professor Michael Eddleston, Pharmacology, Toxicology & Therapeutics, University of Edinburgh Professor Adam Cohen, Centre for Human Drug Research, Leiden
31	German Medicines Manufacturers Association (BAH)
33	Professor Claude Reiss, PhD, former research director with the French National Centre for Scientific Research (CNRS), CEO and research co-director of Vigilant Technologies
34	Ethics Board at Technische Universitaet Dresden, Dresden, Germany
35	British Pharmacological Society

1. General comments – overview

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3	Thank you for the chance to contribute to this discussion. The following is a personal view of an ex-regulator. I think the current 2007 EMA FIM guideline is dangerous. This is because it puts too much emphasis, without adequate recognition of the unknown, on a rational calculation of the first dose in man from the NOAEL and MABEL calculations based on the known toxicology. Sometimes the toxicology cannot provide sufficient predictions of the human effects of a drug. Recent examples provide unfortunate evidence of this. Section 4.3.6 “In order to...justified” Having working extensively in first in man studies for many years, and as a regulator of FIM trials, the key message is that <u>the first dose in man can never be too low</u>. Second, most people do not appreciate the logarithmic nature of the dose response curve. When there is doubt about a novel substance, there is no harm in starting with a dose that is one million times lower than the NOAEL/MABEL prediction in up to three subjects. Rapid increases in exposure, in many cases every 24 hours, can be given if the increases are limited to either a tenfold increase in dose, or up to a tenfold exposure in numbers at each dosing stage. Whenever the first possible safety signal is detected from basic simple monitoring, then increases in either the dose, or the population exposure, but never both at the same time, should be limited to three fold. This approach is likely to have prevented disasters that have occurred with FIM studies at minimal extra cost. The key is to have a log, or semi-log, pyramidal approach to exposure to either the dose, or the population.	The text relating to dosing has been extensively revised including a new section on dosing which outlines principles to support scientifically driven decisions for choice of starting dose levels. A tailored approach for each case is emphasised, taking all available data into account, in a careful manner based on scientific argumentation.
4	I am working as a consultant for the NSW Ministry of Health in Australia on a Framework for early phase	First-in-human/early clinical trials are

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	clinical trials. We would like to make our Framework be as harmonised with agencies such as the EMA as possible. I have just read this document “Concept paper on the revision of the ‘Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products’ (EMA/CHMP/SWP/28367/07) In it I note that you are proposing to expand the definition of the guidance to “Extension of the guidance to early phase CTs including single study or integrated protocol designs” p. 2 “extension of the remit of the guidance beyond single ascending dose FIH trials to incorporate other early phase trials and designs” p.3 I was wondering how/if you were going to explicitly define early phase trials in more detail in the final guidance document?	broadly defined in the revised guideline as including those which generate initial knowledge in humans on tolerability, safety, PK and PD. These trials may also include collection of data on e.g. food or drug interactions, different age groups or gender, proof of concept and relative bioavailability of different formulations. These trials are often undertaken in healthy volunteers but can also be performed (or include) patients.
5	We agree with the agencies assessment of the limitations of the current guidance document and support the decision to revise the document as outlined in the concept paper. Specifically: 1. The current guidance focuses on therapeutics defined as high-risk. As a result of this focus, the guidance does not provide recommendations on FIH studies not categorized as high risk, and these studies still have important safety considerations. In addition, phase 1 studies that are not FIH are also not directly addressed in the current guidance. The revised guidance should be more inclusive and provide guidance on a broader range of studies. 2. The current guidance provides very general information on dose selection that should be expanded upon. 3. The clinical oversight of FIH studies and the appropriate required safety data and review of that data during the study should be emphasized.	The scope has been revised to also cover early clinical trials. An uncertainty-based approach has been introduced throughout the guideline. The issues of consent and source documentation are considered outside the scope of this scientific guideline. There is a statement in the revised guideline that special populations, such as paediatrics, deserve additional specific considerations as per ICH E11.

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	4. Additional recommendations should be provided on the use of PK-PD modelling to guide study design and dosing. We also recommend expanding the current guidance to address topics not discussed in the concept paper. These topics are: A. Informed consent i. Describe the agencies' position on and requirements for electronic consent in FIH studies. ii. Describe the agencies' position on group, video and remote consent (consenting for studies using a secure web portal) in FIH studies. iii. Describe the agencies' position on the use of social media and text messaging to recruit healthy volunteers in FIH studies B. Source documentation i. Describe the agencies' position on and requirements for e-source documentation in FIH studies. ii. Describe the agencies' position on the use of wearable devices for data capture in FIH studies. iii. Describe the agencies' position on the use of electronic health records data (e.g. vital signs, laboratory values, medical history available per standard of care) in Phase 1 studies. C. Pediatric phase 1 studies i. Describe the agencies' position on and recommendations for phase 1 studies in the pediatric population.	
7	The revision of the guideline on the nonclinical data necessary for FIH studies and the revision of the Guideline on strategies to identify and mitigate the risks for First-In-Human clinical trials with	The non-clinical data requirements in support of clinical development are outlined in ICH M3 (R2), ICH S6 (R1),

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	investigational medicinal products should be addressed separately.	ICH S9 and related Q&As as applicable. The revised guideline complements ICH guidance documents and outlines how non-clinical data should be analysed and used to ensure a safe and effective transition to clinical development.
7	The scientific community and regulators should decide if the self-developed practice of the FIH integrated protocols is scientifically correct and, consequently, should be admitted or not.	Not agreed. It is considered that integrated protocols are here to stay. Therefore the guideline is aimed at making FIH/early clinical trials, including integrated trials, as safe as possible.
7	Ethics Committees or other CA with specific expertise in FIH should be organised to review, discuss and approve protocols of 1 st in human studies	Clinical trial approval and related decision making processes are regulated in the EU at the level of member states. Therefore setting specific rules is considered outside the scope of this scientific guidance document.

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8	We have noticed the increased frequency with which the sponsors with whom we work (as cardiovascular safety consults) have proposed first in human (FIH) trials in which they no longer believe that it is necessary or even ethical to continue dose ascension until the maximum tolerated dose (MTD) of the new compound is reached. The increased precision of pre-clinical pharmacodynamic studies has improved the precision of their estimates of the effect clinical dose in humans; as a result, they do not feel that it is appropriate to increase the dose of a new medication beyond the highest dose that they anticipate will be clinically effective. There a number of potential issues which may arise from evaluating only a limited range of doses of a new product during the FIH trials: • Estimates of the effective clinical dose based on translation of preclinical pharmacodynamic data and modeling may significantly underestimate the effective human clinical dose. In such a situation, the FIH tests might incorrectly lead to the conclusion that a new product is inefficacious simply because an adequate dose was never evaluated. • Estimates of human tolerability of a drug based on preclinical toxicology studies may overestimate the safety of the product in humans. For this reason it is critical to apply appropriate precautions and safeguards during dose escalation, especially in multiple dose trials. However, estimates of human tolerability based on extrapolation from preclinical data may also underestimate the human tolerability. In such a situation, the FIH tests might incorrectly lead to the conclusion that a new product is inefficacious simply because an adequate dose was never evaluated. • A recent trend in the evaluation of the cardiac safety of new drugs, and in particular their effect on cardiac repolarization, involves the collection of intense ECG data time matched to PK collections. This allows the use of concentration-QTc effect modeling to assess a new drug's effects on ECG parameters such as QTc, and may potentially obviate the need for a dedicated Thorough QT/QTc trial. When assessing the effects of a compound on cardiac repolarization, regulatory authorities generally require	Issues around dosing were extensively commented upon and a new section has been added to the revised guideline around dosing selection and maximal dose/exposure levels.

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	the evaluation of a "supratherapeutic dose" of the compound in order to inform the effects of the compound for subsets of patients who might be exposed to higher than standard peak exposures. The selection of the appropriate supratherapeutic dose is individualized for each compound, but in general, one seeks to achieve at least a 3-5 fold multiple of the highest clinically relevant exposure (if feasible). In order to avoid the need for a separate positive control to demonstrate assay sensitivity, the required "sufficiently high multiple of the clinically relevant exposure" referred to in the ICH E14 Q&A (R3) might be even higher. This requirement for evaluation of a large multiple of the clinically relevant exposure would require that during FIH trials, dose escalation continue well beyond the anticipated clinical dose and up to a maximum tolerated dose. This regulatory requirement, which is necessary to enable the use of concentration-QTc effect modeling in FIH trials, seems to be in conflict with the goals expressed in the current EMA concept paper on the revision of the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products'. This conflict will unfortunately increase the uncertainty already present for drug developers trying to plan the doses to be evaluated in their FIH trials. Common sense dictates that there is no reason during FIH trials to increase the dosage of a new compound to the MTD simply for the sake of characterizing the highest tolerable dose without regard as to whether there is any practical or scientific value to such data. Dosing decisions in clinical trials, and especially in FIH trials, must be based first upon concerns for human safety, and second on investigational needs. However, as we have attempted to point out, there are a number of potentially very valid reasons during FIH trials for evaluating doses of a new compound that are higher than the dosage predicted based on preclinical data. Drug development, especially during the early phases, requires balancing many divergent, potentially conflicting needs, and therefore requires thoughtful, prudent decision making on a compound by compound basis.	

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9	It's not clear whether any phase I Principal Investigators (PIs) will be involved in the redrafting of the guidance. We'd strongly recommend that academic and industry PIs be involved. PIs are key stakeholders, as they are experienced in managing first-in-human clinical trials and are responsible for safety of trial participants.	All stakeholders were invited to contribute to the revision through public consultations on the concept paper and on the revised draft. The major areas of interest were also discussed at a workshop on the revision of the guideline hosted at the EMA.
10	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 pivotal studies assessing the safety and effectiveness of new products – as well as post-approval and pharmacovigilance research. With 9,000 employees engaged in research activities in the UK, over 33,000 in Europe, and more than 120,000 worldwide, ACRO member companies advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 pharmaceutical, biotech, and medical device sponsors of clinical trials each year. ACRO welcomes and strongly supports the proposal to revise the current guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. ACRO agrees with the various discussion points identified in section 3 of the Reflection Paper but, as noted below, considers that recommendations in the report of the Temporary Specialist Scientific Committee established by the French competent authority (ANSM) into the BIA 10-2474 clinical trial, conducted in Rennes, in January 2016 should also be addressed specifically in the revised guideline.	Some of these comments made are out of the scope of the guideline and in the remit of national competent authorities. Lessons learned from the trial in Rennes will be taken into account but the revision of the guideline has a broader intent and is aimed at keeping early phase clinical trials safe in the first place building on experience since the first guideline was published and to provide guidance with regard to current practice. Consistency with ICH and other guidelines was carefully considered during the revision.

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	Additionally, while recognizing that this is outside the scope of the Concept Paper, which is concerned with revision of the current guideline, ACRO notes that the <u>voluntary</u> accreditation programme for Phase I units in the UK, established by the UK competent authority (MHRA), has led to improvements in the identification and mitigation of risks to subject safety in human pharmacology studies conducted in accredited units. ACRO therefore suggests that the EU regulatory network (EMA, national medicines agencies, and the European Commission) consider studying the utility of the MHRA's voluntary accreditation programme. In addition to an EMA guideline, ACRO asks the Agency to consider if it would be beneficial to harmonise these guidelines globally and include them in, for instance, ICH M3 (R2). The guideline does not mention what risk level, after risk mitigation, is acceptable for FIH studies. This is difficult to define, but ACRO asks the Agency to consider, for example, if it would be helpful to note that the risk resulting from hazard identification and risk mitigation should be minimal and comparable with risk for an activity which is accepted by the society. Before proceeding to "Section 2" of this comment ("Specific Comments on Text"), there are five discussions omitted from the current Concept Paper which ACRO believes merit inclusion in the revised guidance. First, ACRO recommends that the recommendations in the report of the Temporary Specialist Scientific Committee established by the French competent authority (ANSM) into the BIA 10-2474 clinical trial, conducted in Rennes, in January 2016 should also be addressed specifically in the revised guideline. This can be done via addition of the following bullet points: • "the need for sufficiently comprehensive preclinical pharmacological studies on a sufficiently broad dose range so as to be reasonably predictive of real life, future therapeutic efficacy." • "the need for specific assessments during volunteer screening targeted to the pharmacological	Issues around dosing were extensively commented upon and a new section has been added to the revised guideline around dosing selection and maximal dose/exposure levels.

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	profile of the drug, as determined by preclinical and prior human studies.” • “dose adjustments in human pharmacology trial protocols based on all of the data previously collected in humans.” • “the circumstances in which sequential dosing regimes, currently used in single ascending dose studies in human volunteers, should be extended to multiple ascending dose studies.” Second, ACRO asks the Agency to consider the following content on dose escalation. If the inhibition of a biomarker is employed as an indicator of drug activity, then the rationale for dose escalation above the point of complete inhibition of the biomarker should be stated in the protocol. Additionally, ACRO considers that, where a drug shows little or no evidence of toxicity in early human studies, it is not necessary to continue ascending doses (either single or multiple doses) to establish a maximum tolerated dose. ACRO recommends that trial protocols should prospectively establish a multiple of the anticipated therapeutic dose (sufficient to provide an adequate safety margin) that will not be exceeded in the absence of adverse effects. To achieve this, ACRO suggests the addition of the following statements: “Consideration should be given to creating a requirement for justification of escalation above the dose level at which a relevant biomarker is completely inhibited in the absence of a detectable physiological signal. Consideration should also be given to establishing a multiple of the therapeutic dose (sufficient to provide an adequate safety margin) that will not be exceeded in the absence of adverse effects. This maximum dose should be stated prospectively in the protocol for the human pharmacology trial.” Third, a discussion of the use of sentinel dosing would be helpful. ACRO suggests including content stating that all studies involving compounds determined to be at risk include sentinel dosing of 2 subjects for at least the first few cohorts, if not all. And, the sentinel cohort(s) should force randomization to result in an active and placebo treatment assigned within the cohort. Finally, the wash between dosing, safety assessment, and progression to dosing of the balance of the cohort should exceed 24 hours or at least 1 half-life, whichever is longer. Included in this decision should also include careful evaluation of the	

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	expected physiologic effects in humans as well as any pre-clinical evidence that suggests the compound may induce or potentiate immunological reactions. Fourth, ACRO asks the Agency to consider a program of enhanced communication with the Member State regulatory authorities. If a previous FIH clinical trial is suspended or terminated due to lack of detectable activity or due to adverse effects in human volunteers, this information may not be known to the Ethics Committee and regulatory authority in the Member State responsible for reviewing a protocol for another mechanistically-similar agent, or to the sponsor of the trial. However, the information is known to the EMA. ACRO asks the Agency to consider establishing a process whereby Member States can refer FIH trials to the EMA to ascertain (a) whether previous trials with mechanistically-similar agents have been terminated or suspended, and (b) the reason for that. If the reason relates to lack of detectable activity, despite the use of doses which maximally inhibited the biomarker, then the sponsor of the proposed study should be required to explain the reasons for proceeding with that study. If the reason relates to safety, then the safety considerations from the previous study or studies should be taken into consideration in the design of the proposed study. If an FIH study is suspended or terminated, there is no obvious route whereby that information might become known to the sponsor of another FIH study involving a mechanistically-similar molecule, or to the Ethics Committee and regulatory authority in the Member State which approved the latter study. Would it be possible for the EMA to establish a process whereby FIH which are suspended or terminated can be made known to Ethics Committees and regulatory authorities in all Member States which have approved FIH trials involving agents with similar mechanisms. Would it be possible to create a requirement for Ethics Committees and regulatory authorities which receive such information to review it and provide reasons in writing (to be used in any subsequent investigation should the need arise) for their decision regarding continuation, modification or termination of the later trial. Fifth, for combined-design studies, e.g., SAD-MAD, the requirements for repeat-dose preclinical studies are ambiguous. ACRO asks the Agency to consider whether particular sections of ICH M3 (R2) should be	

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	codified in a manner similar to ICH E6, such that appropriate durations of preclinical exposure are required as a condition of approval for FIH trials. For SAD/MAD designs consider recommendation to require complete safety review prior to escalating to next dose. This is usually included in studies, but on occasion less experienced sponsors will bypass this requirement.	
11	I do get the impression that some FIH-trials or CT may be preceded by very early first individual therapy attempts. I am not sure about that but specifically in non-industrial drug development following “urgent needs” before being able to start a sound FIH trial has to be expected. It might therefore be discussed when and under which preconditions such individual experiences and case reports would be acceptable. It might further be discussed how such experiences should be reported and involved in upcoming FIH-trials.	A tailored, uncertainty-based approach for each trial is emphasised in the revised guideline, taking all available data (both non-clinical and exploratory clinical data) into account, in a careful manner based on scientific argumentation.
12	The Edinburgh Phase I / First in Human Study Review Committee (PISRC) conducts scientific review and clinical risk assessment of Phase I / FIH studies submitted for conduct in Edinburgh Clinical Research Facility, which is an accredited unit under the MHRA Phase I Accreditation Scheme. The PISRC recognise that the design of FIH and early phase clinical trials has evolved considerably since the publication of the EMA paper ‘<i>Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products</i>’. The PISRC also feel strongly that the lessons learnt following the BIA-102474-101 clinical trial in France, which ended tragically in January 2016, should be incorporated into the EMA’s guidance. The PISRC therefore welcome the proposed revision of the guideline and appreciate the opportunity to comment on it. The PISRC are largely in agreement with the aspects of the guideline that have been highlighted for discussion within the concept paper. The comments in this submission are mostly general in nature and are described below: 1. Emerging clinical data, including PK and PD data, should be reviewed more closely and consistently	Some of these comments made are out of the scope of the guideline and in the remit of national competent authorities. Lessons learned from the trial in Rennes will be taken into account but the guideline has a broader intent and is aimed at keeping clinical early phase trials safe in the first place building on experience since the first guideline was published and to provide guidance with regard to current practice. A tailored, uncertainty-based approach

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	throughout the study than is often currently seen. Trends in this data may highlight potential safety issues that would not be picked up through review of SAEs alone, and could therefore be crucial to decisions regarding the continuation and ongoing management of the study. Robust review of all available PK and PD data, which must include those from the preceding dose, should be undertaken prior to any dose escalation decision. 2. Although safety is the primary consideration in FIH and early phase clinical trials, importance should also be placed on understanding the human pharmacology of the IMP, and in particular how this relates to safety aspects. Clinical data on the biological effects of the IMP (pharmacodynamics) should therefore be monitored and taken into account in addition to toxicity and adverse event data. It should not be acceptable for a trial to be designed to establish the maximum tolerated dose, without any consideration of dose-response. Escalation of the dose beyond the level at which there is unlikely to be any further increase in potential therapeutic benefit is unethical and should not be supported. 3. The welcome and important extension of the guidance beyond SAD FIH trial designs should take potential variation between subject groups into consideration. A similarly cautious approach to starting dose and dose escalation, including the use of sequential dosing, should be taken each time the IMP is introduced to a new subject group, e.g. moving into a different age range, moving from healthy volunteers into patients, etc. It cannot be assumed that the effect seen in one subject group will be mirrored in another. 4. Guidance on who is considered appropriate to undertake review of emerging clinical data would be welcomed. In many cases the competent authority gives authorisation for a complex, multipart clinical trial with an integrated protocol based only on the non-clinical data submitted as part of a single CT application. Ongoing monitoring of emerging data, and subsequent decisions regarding progression of the trial to later parts, are thereafter often entrusted to a data monitoring committee, or similar body, appointed by the sponsor. The PISRC believe strongly that measures should be in place to ensure such review bodies have the necessary expertise and should be independent of the sponsor, and that this	for each trial is emphasised in the revised guideline, taking all available data into account, in a careful manner based on scientific argumentation.

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	should be reflected in the guideline. Consideration should also be given to extending and reinforcing the requirements for the ongoing involvement of competent authorities and ethics committees in reviewing emerging data, including SAE and SUSAR data, in relation to progression of the trial to higher and/or multiple doses. 5. Measures within the guideline to encourage greater transparency and access to emerging clinical data for investigators and independent review bodies would be welcome.	
13	On behalf of the International Plasma Fractionation Association (IPFA) I thank you for offering the opportunity to comment on the EMA Concept paper on the revision of the Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products, EMA/CHMP/446302/2016. After consulting the IPFA member organisations, I can inform you that we have no comments on this document.	General agreement.
15	Quotient Clinical Ltd., an early Phase development Company, welcomes the opportunity to provide comments on the Concept paper on the revision of the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products' (EMA/CHMP/SWP/28367/07). It is unclear whether any Phase I Principal Investigators (PIs) will be involved in the redrafting of the guideline. We strongly recommend that academic and industry PIs be involved. PIs are key stakeholders, as they are experienced in managing first-in-human clinical trials and are responsible for safety of trial participants.	All stakeholders were potentially involved through a public consultation and a workshop on the revision of the guideline.
16	We hereby would like to draw your attention to the fact that phytomedicines and medicinal products of other traditions, e. g. homeopathy or anthroposophic medicine, are often based on complex compounds such as plant extracts, for instance. Therefore it could be necessary to take into account that for these medicinal products one single active substance with clear preclinical data can only seldom be identified. Consequently, overall risk assessment for FIH and early CT administration as well as translation of non-clinical data to human use by extrapolation on the basis of PK- and PD-data will only in rare cases be	The issue is addressed in the scope of the revised guideline which applies to all new chemical and biological IMPs. A statement has been added in the introduction however that as IMPs are widely different in their

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	possible for these medicinal products. We therefore ask you to consider the special characteristics of phytomedicines and medicinal products of other traditions based on complex compounds in the revision of this guideline.	pharmacological features and intended use different parts of the guideline may be important for some and inapplicable to others.
18	IQ welcomes the Agency proposal to update the “guideline on strategies to identify and mitigate the risks for first in human clinical trials with investigational products” to account for integrated clinical trial (CT) designs. Many of the proposals in the concept paper represent current industry best practice; however IQ is concerned that the proposed update may lead to an overly prescriptive guidance and urges the Agency to ensure flexibility in requirements for nonclinical pharmacology (data generation, integration and translation), clinical trial design (e.g. combining SAD/MAD and other elements into FIH protocols) and approval/amendments are maintained. Overall, IQ member companies believe there is not a “one size fits all” application for many of the areas identified in the EMA Concept paper and thus continue to support the adoption of a risk-based approach when considering the application of additional safe guards for first human studies. The EMA is asked to: 1) clarify whether the scope of the revision will include gene and cell based therapies previously excluded from the 2007 guideline; 2) confirm whether the additional precautionary measures outlined in the concept paper apply to all CTs or just those where additional special safety considerations (as outlined in the Factors of Risk section [section 4] of the original 2007 guideline) are identified. IQ member companies support a risk-based approach and appropriate use of risk mitigation strategies rather than their use as a default, in all instances, and in all CTs irrespective of the risks. 3) confirm whether the scope of the revised guidance includes CTs in patients (including patients with debilitating and life-threatening diseases such as oncology), as well as healthy volunteers. Patients with	See above re ATMPs and scope. A tailored, uncertainty-based approach for each trial is emphasised in the revised guideline, taking all available data into account, in a careful manner based on scientific argumentation. The scope covers patients and healthy volunteers.

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	debilitating and life threatening diseases have a short life expectancy and their quality of life is greatly diminished, despite available therapies (e.g. oncology). If these patient populations are included within the scope of the revised guideline, then the guidance must recognise and reflect the need for far greater flexibility in the nonclinical requirements and clinical trial design/conduct to account for the differences in benefit-risk profile relative to healthy volunteers. IQ member companies would therefore recommend that debilitating and life-threatening diseases (such as oncology) are outside the scope of the revised guideline. If CTs for debilitating and life-threatening diseases (e.g. oncology) are within the scope of the guidance, then IQ member companies suggest that the EMA consider how newer strategies such as adaptive design (incorporation of Bayesian models) might support dosing strategies, including dose escalation, since such approaches, when used properly, can reduce necessary numbers of trial participants and may more precisely define maximum doses/exposures. IQ encourages the Agency to follow the same approach as in the 2007 guidance for entry-into-human studies, which provided a description of the factors that need to be taken into account and basic guidance on phase I studies. Because this area is rapidly evolving, inflexible and narrow requirements may quickly become out-of-date. The Agency is also encouraged to consider the potential negative impact of overly prescriptive requirements in encumbering the drug development process, particularly in areas of high unmet medical need such as oncology and other severely debilitating or life-threatening diseases. General Non-clinical Comments: Although considerable advances have been made in the translatability of nonclinical models in some areas, such as oncology (Wong et al 2012) and antibacterials, the lack of translation to desired clinical outcomes based on animal pharmacology data is still recognized as a key contributor to drug development failures (Hay et al 2014). Indeed the value of nonclinical models in many therapeutic areas is questionable for efficacy and target exposure.	

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	While there is great value in adequately exploring nonclinical PK/PD and its translation to support clinical dose selection, limitations in nonclinical models may prevent such relationships from being readily defined. For instance, definition of PK/PD may be challenging in pharmacology models that do not directly recapitulate the human disease state or scenarios where only surrogate efficacy biomarkers are available. In such cases, it may not be possible to conclusively identify target efficacious clinical exposure levels. Additionally, the translatability of on- or off-target safety findings may be difficult to define during initial stages of clinical development. As the predictivity of nonclinical pharmacology models across different therapeutic areas and indications can vary widely, updates to the guidance should provide flexibility and recommendations for situations in which nonclinical safety and/or pharmacology data may be limited. Consequently, the guidance should reflect the need for flexibility in the nonclinical data required to support FIH and acknowledge the data may include in vitro or in vivo nonclinical data and/or human genetic data sufficient to support the conclusion that the intended pharmacology should have a positive impact on the disease progression or end state. IQ considers that because of the limitations in translatability of nonclinical models for many therapeutic areas, the guidance should accommodate exploratory clinical trials as described in ICH M3 (R2). This allows earlier and more efficient clinical evaluation of PK, PD, and other biomarkers of target engagement. IQ requests that new guidance should remain consistent with timing of studies and requirements for testing outlined in ICH M3 (R2). The EMA is asked to consider the inclusion of a discussion around how prior nonclinical and clinical data and knowledge around target biology can suggest on-target class effects and therefore might influence FIH study designs and safety monitoring. Demonstration of in vitro selectivity, specifically against a broad and diverse panel of related targets when available, should be an expectation for small molecules. Since these will usually involve human targets, this will bolster the safety assessment of molecules and complement the safety package in preclinical species.	

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	Clinical Trial Design Comments: Regarding the proposal to address integrated CT designs and study endpoints, including rolling review of emerging human data during the study, it is acknowledged that contemporary FIH trials often include multiple study parts designed to address a number of research questions. Such innovation in FIH studies has occurred in part due to technological advances in data capture and cleaning, programming, analysis, and communication. In addition, modern bioanalytics allow for rapid turnaround of pharmacokinetic data (and PD/efficacy biomarker data in many cases). Such advances allow for a thorough and timely review of safety and PK data for immediate decision-making. The benefits of such integrated approaches allow Applicants to answer many scientific questions as efficiently as possible, in many cases minimizing the number of healthy subjects exposed to study drug. In most cases a multi-part FIH study may be designed and executed with frequent and thorough review of emerging data to make real-time decisions at no additional risk to subjects. Thus, the Agency is encouraged to ensure that clinical protocols still have the flexibility to respond to emerging data without the need for an amendment, potentially with a decision tree used to guide the trial's progress. Addressing questions about the effect of formulation on drug bioavailability, food effect, the potential for drug-drug interactions, or early proof-of-principle as part of a single FIH trial fulfils a dual purpose of minimizing unnecessary study drug exposure in healthy subjects, while improving early decision-making to allow the most promising candidates to move forward safely into patients in a timely manner. It is important the guidance acknowledges the value of such integrated approaches and encourages sponsors to design studies with efficiency in mind. Including examples of smart integrated study design in the guidance would be valuable for promoting a more innovative approach to early drug development. Regarding the aspect of rolling review of emerging data and pre-defined dose/exposure range and stopping rules, it is important that for dose escalation to proceed in a safe and efficient manner, FIH protocols contain flexibility in this regard. It most cases it is appropriate for doses to be selected in real-time as the study proceeds, based on emerging data. However, it is understood that Sponsors should	

Stakeholder no.	General comment	Outcome (if applicable)
	provide some framework for how rapidly doses may be escalated and on the basis of what data, as well as appropriate stopping rules in the protocol, based on the preclinical safety and other compound-specific information. References: Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. <i>Nature Biotechnology</i> 32, 40–51 (2014). Wong H, Choo EF, Alicke B, Ding X, La H, McNamara E, Theil FP, Tibbitts J, Friedman LS, Hop CE, Gould SE. Antitumor activity of targeted and cytotoxic agents in murine subcutaneous tumor models correlates with clinical response. <i>Clin Cancer Res.</i> 2012 Jul 15;18(14):3846-55.	
20	The European Federation for Early Medicines Development welcomes the opportunity to submit these comments and observations on the European Medicines Agency's <i>'Concept paper on the revision of the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products'</i> (EMA/CHMP/SWP/28367/07), issued for public consultation. Introduction of EUFEMED EUFEMED is a “European voice” for exploratory medicines development; the Federation consists of four national associations: AGAH (Germany), AHPPI (UK), BAPU (Belgium) and Club Phase 1 (France). • EUFEMED is a European not-for-profit federation of associations involved in early clinical development of new medicines. • Members of the founding societies are all professionally active in exploratory clinical trials in healthy participants, special populations and patients. Members are: ➤ Academics	As stated above, all stakeholders were potentially involved through a public consultation and a workshop on the revision of the guideline. Also as above, a tailored, uncertainty-based approach for each trial is emphasised in the revised guideline, taking all available data into account, in a careful manner based on scientific argumentation.

Stakeholder no.	General comment	Outcome (if applicable)
	➤ Investigators ➤ Pharma or Biotech companies ➤ Service providers • The Federation's main purpose is to support exploratory medicines development in Europe by: ➤ Sharing expertise of its members ➤ Organising conferences and training sessions (next conference "Exploratory medicines development - Innovation and risk management"; 17 to 19 May 2017, London) ➤ Developing standards to improve European competitiveness Overview General Comments Section - Feedback on the discussion points stated in the concept paper. - Proposals: (a) To involve experienced European early phase Principal Investigators as stakeholders into the drafting of the revised guideline. (b) The revised guideline should allow justified flexibility in the application of its prescribed risk management, trial design and trial conduct processes, to account for the different types of early phase clinical trials and the Investigational Medicinal Products used. Feedback on the discussion points stated in the concept paper EUFEMED agrees with the discussion points outlined in the concept paper. The points cover the breadth of considerations made - depending on IMP and trial design - , when designing and conducting early phase	

Stakeholder no.	General comment	Outcome (if applicable)
	trials, including those that integrate multiple parts into one combined protocol. Proposals: (a) To involve experienced European early phase Principal Investigators as stakeholders into the drafting of the revised guideline. EUFEMED represents – amongst others - European early phase investigators, who have extensive experience conducting integrated early phase clinical trials. The discussion points outlined in the concept paper have been regularly applied by these investigators in clinical practice. We propose that the EMA draws on this expertise by including a group of experienced early phase investigators as key stakeholders into the drafting of the revised guideline. (b) The revised guideline should allow justified flexibility in the application of its prescribed risk management, trial design and trial conduct processes, to account for the different types of early phase clinical trials and the Investigational Medicinal Products used. Early phase trials vary greatly in design and in the nature of the compounds investigated. Whilst the revised guideline should be comprehensive in stating potential risk management considerations for early phase trials, there are types of trials for which few apply. Therefore the guideline should allow sponsors' and investigators' clinical judgement in the guideline's application on a trial-by-trial basis. To ensure an efficient and competitive European process, the guideline should explicitly advocate a focussed description of risk management, based solely on trial-relevant risks and their management. Such a risk-based approach would be in keeping with the spirit of adaptive, integrated trial design, for which flexibility within set, trial-specific boundaries is a pre-requisite.	

Stakeholder no.	General comment	Outcome (if applicable)
21	The concept paper indicates that changes to the recommended design and conduct of first-in-human (FIH) studies are to be proposed, and we appreciate the opportunity to comment on possible improvements. We do not believe there is routinely a need to establish the maximum tolerated dose in early phase studies where subject safety may be compromised by this objective, especially where pharmacodynamic (PD) data suggest that a maximal useful pharmacological effect versus the intended target has been approached. We were also concerned that when the serious events in a FIH study conducted in France (BIA10-2474) were publicly reported, we and other early clinical investigators were unable to assess possible implications for subject safety in our own ongoing studies because we were unable to access the protocol or investigational brochure (IB) because of commercial confidentiality. We envisage emphasis on possible requirements for: • more rigorous preclinical pharmacology data underpinning: 1. a convincing rationale for anticipating efficacy; 2. more rigorous evidence of “down stream” toxicity (both on- and off-target), especially where dealing with a new biological target or a target with limited physiological understanding in man 3. where possible a rigorous preclinical understanding of the activity of main metabolites, with pharmacokinetics (PK) of such metabolites in the clinical studies identified in the protocol as part of dose-escalation decisions where relevant. • wider application of sentinel dosing strategies (eg to multiple dose cohorts in some circumstances, especially where emerging data indicate the likelihood of a steep dose response curve, drug accumulation or of non-linear kinetics). Such requirement will need to be flexible to take account of the PK and PD of individual drugs, and to avoid unnecessary delay to the development process. • consideration by the safety review committee of available real time PK and PD data (ie from subjects dosed to date), in addition to safety data, before dose escalation decisions • appropriate clinical and PD assessments should be defined in the protocol, taking into account the	As stated above, a tailored, uncertainty-based approach for each trial is emphasised in the revised guideline, taking all available data into account, in a careful manner based on scientific argumentation. The issues raised here including sentinel dosing and stopping rules were extensively raised and addressed in the revised guideline. Issues around access to documents are outside the scope.

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	potential activity and the ADME profile of a new molecule. • protocols should encourage a cautious approach to dose increment decisions by the safety review committee. Depending on the preclinical studies and anticipated pharmacologically active dose in man dose escalation in a geometric series (e.g. two-fold steps) may not be appropriate as the maximum permissible dose is approached • protocol-defined selected planned doses should be based on the required level of information to move to the next stage of development of the IMP, rather than attempting to define a maximum tolerated dose • unambiguous stopping or dosing pause rules, especially around the occurrence of SAEs/SUSARs • before granting approval to proposed studies, research ethics committees as well as the regulatory authorities should consider the desirability of requiring sponsors and CROs routinely immediately to make available protocols and IBs in response to serious adverse reactions that result in study discontinuation, and requiring that transparency should outweigh confidentiality in such circumstances. Early clinical development studies are particularly appropriate for an adaptive design. Although pre-clinical data can be thorough and extensive, animal studies are not always predictive of what happens in man (e.g. TGN1412 and BIA10-2474). Consequently, once in man, it is essential to review the emerging human data (safety, PK and PD) in real time to make the appropriate decisions in terms of any changes to the planned dose escalation and future clinical assessments. It is critical that this review is described in detail in the study protocol including a clear and unambiguous process for decision making and in particular rules on when to pause (or temporarily halt) the study and when to stop a study. In our own units we have been applying this approach for FIH studies and have not found this to be over burdensome. As subject safety is paramount and with the inclusion of more patients in early phase studies, we believe these suggestions will help investigators and sponsors to optimise decision making, while accepting that they may increase the time and cost. This investment in facilitating appropriate safe,	

Stakeholder no.	General comment	Outcome (if applicable)
	timely and efficient decision making, appears proportionate in the context of a 7 years average clinical development phase and overall >\$2 billion cost of bringing an investigational medicinal product (IMP) to market. We thank you again for the opportunity to express these comments,	
22	I am Head of the Clinical Investigation Center (CIC) Paris-Est at Pitié-Salpêtrière University Hospital in Paris and have closely followed the BIA 10-2474 case. I believe important things have not been written about the consequences of this case and have written an Editorial with Prof Joël Ménard, which just came out (https://www.ncbi.nlm.nih.gov/pubmed/27666586). Namely: - the need for investigators training (to medicine rather than to following procedures) - the need to share information about early phase trials more extensively than currently done - the change of paradigm for MTD determination in FIH studies Although these topics are not the main target of the concept paper currently in discussion at EMA, http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500210825&mid=WC0b01ac058009a3dc, I am sending our editorial in case clinical aspects of FIH are under discussion among regulatory authorities.	Contents of the editorial noted.
23	EUCROF welcomes the opportunity to provide comments on the European Medicines Agency's <i>'Concept paper on the revision of the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products'</i> (EMA/CHMP/SWP/28367/07), issued for public consultation. Overall EUCROF is aligned with the main discussion points listed in the Concept paper that are to be covered during the review of the current guideline. It is important that the new guideline, whilst providing a robust and safe framework, retains sufficient flexibility to ensure the continued ability to undertake	As stated above, a tailored, uncertainty-based approach for each trial is emphasised in the revised guideline, taking all available data into account, in a careful manner based on scientific argumentation.

Stakeholder no.	General comment	Outcome (if applicable)
	clinical research using a variety of adaptive and integrated approaches, which are often vital in the early stages of a drug's development. To this end we would propose that the EMA take the opportunity when preparing the revised guidelines to specifically seek the input from both academic and industry Principal Investigators. These are the individuals who have the most relevant experience in progressing first in human clinical trials and have the ultimate responsibility for the safety of trial participants. This may already be planned but is not clear from the Concept paper. In due course, our members look forward to the publication of the revised guideline for comment.	
24a	1. The paper would benefit from some discussion of pharmacogenomics. If there is a risk of differential behaviour as a result of genetic factors then the researchers should consider how to adapt the study to take this into account, either to mitigate risk or in an exploratory manner to understand what has happened.	The revised guidance genetic factors under 8.2.3.
24b	2. Similarly immunogenicity should be addressed i.e. how to identify whether there are pre-existing antibodies to the therapeutic agent or if the therapeutic agent induces such antibodies and how to mitigate this.	This is considered too specific for a general guideline.
24c	3. Consideration might be given to how the recommendation in EMEA/CHMP/SWP/28367/07 that: "healthy subjects or patients should not be included in first-in-human clinical trials if they are in another clinical trial or have participated recently in another clinical trial unless justified. It is important to include clear exclusion criteria to prevent concomitant or immediate consecutive exposure to investigational medicinal products" might be facilitated. For example, In the UK, the HRA hosts The Over-volunteering Prevention System (TOPS) which aims to prevent participants from taking part too frequently in trials of new medicines. Volunteers are registered on TOPS when they attend a unit for a screening exam. Once the volunteer is registered on TOPS, other units using TOPS will be able to see that the volunteer has attended the unit and may be intending to participate in a study. It is a standard condition of ethical approval, as well as part of the MHRA accreditation scheme, that all Phase I studies using healthy	This is considered outside the scope of this scientific guideline.

Stakeholder no.	General comment	Outcome (if applicable)
	volunteers register research participants onto TOPS and complete the record for each volunteer to specify whether they received a dose of the study medicine. It is free to all UK organisations undertaking Phase I trials in healthy volunteers.	
25	EFPIA 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 earlier this year in France. Therefore, we welcome this opportunity to comment on this CHMP Concept Paper and provide proposals for revision of the First in Human (FIH) guideline. Through a thorough internal look across many therapeutic areas and processes, we believe there is opportunity for the EMA to craft additional guidance for industry to consider in preparation for, and in conducting first in human trials. In doing so, we believe that there is not a “one size fits all” application to many of the areas identified within the EMA Concept paper. By this we strongly believe that a risk-based approach is the direction the EMA should take as they consider application of 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 this risk-based approach should then also be backed up by a scientific, evidence based application to any proposed guidance change. 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 First in Human 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	As stated above, a tailored, uncertainty-based approach for each trial is emphasised in the revised guideline, taking all available data into account, in a careful manner based on scientific argumentation.

Stakeholder no.	General comment	Outcome (if applicable)
	(see Sentinel Dose discussion, below). Therefore, 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.	
25	While we agree the “Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products” should be revised, the revised guidance should clarify and not contravene or contradict ICH M3(R2), including ICH M3(R3) micro-dose strategies.	See above re consistency with ICH guidelines.
26	All the partners of the REGenableMED project are aware of the existence of this draft Guidance. We welcome the opportunity to review this Concept paper on the revision of the ‘Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products’.	General agreement.
27	We understand the trigger for the update of this Guideline has been the incident at Biotrial, along with the fact that the guideline is 10 years old and FIH studies have evolved since then. We would like to underline the many trials that have been conducted successfully, including many integrated SAD-MAD designs and seamless dose determination-expansion designs (for non-oncology and oncology programs respectively). In addition to the proposals in this concept paper, one additional element to ensure safety of FIH studies conducted by Novartis, is the review of an independent internal board (members not in the project team) prior to finalisation and submission of CTA's and IND's for FIH studies. Such a process could be advocated as well. While not exactly the same intent or scope, an analog could be “Safety Assessment Committee” framework outlined in the FDA draft Guidance for Industry released in 2015 (<i>Safety Assessment for IND Safety Reporting</i>). It is also important that the guideline acknowledges and differentiates the requirements for trials conducted in life-threatening/seriously debilitating diseases with high unmet medical need, e.g. advance cancer, as in such settings more flexibility should be applied, as already recognized by regulators in other guidance documents e.g. ICH S9 guideline. We have contributed also on an EFPIA version with comments to this concept paper, which you will receive separately. The	Sponsor processes prior to submission of a CTA are outside the scope.

Stakeholder no.	General comment	Outcome (if applicable)
	comments included below reflect the most important aspects that, in Novartis' view, could be considered in the update of the draft guidance.	
28	Following the dramatic accident which occurred during the course of the First-in-Human study with BIA10-2474, despite an apparent compliance with the current state of the art and moreover the current guidelines in force regulating this step of drug development, (including ICHM3(R2) - 11 June 2009), it is deemed necessary to revise them to prevent such events. The Club Phase I (A French association created more than 20 years ago whose members are individuals involved in the early clinical drug development) is proposing evolution of the current guideline focused on <u>3 main topics</u> (1) Reversing the concept of “Risk Factor” toward a risk-based approach, meaning a by default risk, whatever its identification from non-clinical data, mechanism of action and novelty. Consequently risk mitigation has to be considered, unless risk is alleviated by a comprehensive and extensive set of non-clinical data. (2) Beyond the actual pre-requisite, a more comprehensive and integrated non-clinical package is needed, to alleviate or identify risk factors, a. Using new but now mature simulation tools based on biomarkers of target engagement/modulation, target distribution human vs animal, translational safety biomarkers, Physiologic Based Pharmacokinetics (PBPK), pharmacokinetic / pharmacodynamics (PK/PD) relationship and modelling & simulation. b. In addition a better and more systematic qualitative and quantitative data on potential off-target activities should be requested, including metabolites, with a special emphasis on reversible / irreversible interactions. c. Regarding metabolites, the 10% limit should be revised, in the view of identifying reactive metabolites even if below 10%.	As stated above, a tailored, uncertainty-based approach for each trial is emphasised in the revised guideline, taking all available data into account, in a careful manner based on scientific argumentation. The issues raised here including dosing were extensively raised and addressed in the revised guideline. Reference to microdose studies is included in the revised guideline.

Stakeholder no.	General comment	Outcome (if applicable)
	d. Again if the data provided are insufficient or doubtful the risk mitigation should be applied. (3) Points to consider on the conduct and execution of first in human studies in the context of risk mitigation a. Micro-dosing and low dose under the framework of “exploratory clinical trials” (per ICH M3R2 – June 2009) to be more considered b. Single Ascending Dose (SAD) sentinel subject is a given (meaning one active & one placebo to maintain the blind) c. SAD online data (for dose n+1 or n+2) to support dose escalation: pharmacokinetics and biomarkers of target engagement / safety biomarkers d. SAD top dose to be driven by simulation of exposure and activity (BM) in multiple dose, with a margin integrating a scientifically-based worst exposure scenario (see below §g) up to x10 fold e. Multiple Ascending Dose (MAD) cohorts should be divided in subgroups (generally 2) depending on risk mitigation (i.e. 3 to 6 subjects including at least one placebo). In most cases with a lag time of achievement of steady state between these sub-groups. In case of monoclonal antibody, or drug with a long half-life, staggering of subjects may occur earlier than until steady state is reached. f. MAD data online for dose n+1, Pharmacokinetic (to secure potential supra-linearity) and BM of target engagement/modulation ; g. MAD top dose, if not limited by safety, to be driven by pharmacokinetics and biomarker of target engagement but with a safety margin to build the benefit-risk ratio and identify potential target organ in human. Such margin beyond the desirable level of target	

Stakeholder no.	General comment	Outcome (if applicable)
	engagement should be based on potential worst case scenario exposure (special population and drug-drug interaction) with a clear rationale based on PBPK (e.g. x2 to x10) and the potential usefulness of this dose in the development of the compound. h. Specific inclusion criteria should be driven by mechanism of action and not by default i. For the dose escalation process / decision in both SAD and MAD, clear and detailed rules as well as people and expert involved should be pre-specified. In some case Independent Data and Safety Monitoring Board (DSMB) should be considered.	
29	The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our Joint Specialty Committee for Clinical Pharmacology and Therapeutics and would like to make the following comments. Our experts believe that the current 2007 EMA FIM guideline is potentially unsafe. This is because it puts too much emphasis on a rational calculation of the first dose in man from the NOAEL and MABEL calculations based on the known toxicology. Sometimes the toxicology cannot provide sufficient predictions of the human effects of a drug. Recent examples provide unfortunate evidence of this. In particular, in Section: 4.3.6 Estimation of the first dose in human. 'In order to further limit the potential for adverse reactions in humans, a safety factor may be applied in the calculation of the first dose in human from the MABEL. This should take into account criteria of risks such as the novelty of the active substance, its biological potency and its mode of action, the degree of species specificity, and the shape of the dose-response curve and the degree of uncertainty in the calculation of the MABEL. The safety factors used should be justified. When the methods of calculation (e.g. NOAEL, MABEL) give different estimations of the first dose in man, the lowest value should be used, unless justified.' Our experts have worked extensively in first in man studies and as a regulatory of FIM trials, they note that the key message is that the first dose in man can never be too low. Second, most people do not appreciate the logarithmic nature of the dose response curve. When there is doubt, our experts note that	Issues around dosing were extensively commented upon and a new section has been added to the revised guideline around dosing selection.

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	there is no harm in starting with a dose that is one million times lower than the NOAEL/MABEL prediction in up to three subjects. Rapid increases in exposure, in many cases every 24 hours, can be given if the increases are limited to either a tenfold increase in dose, or up to a tenfold exposure in numbers at each dosing stage. Whenever the first possible safety signal is detected from basic monitoring, then increases in either the dose, or the population exposure, but never both at the same time, should be limited to three fold. Our experts believe that this approach is likely to have prevented disasters that have occurred with FIM studies at minimal cost.	
30	We are clinical pharmacologists who perform and review clinical trials, including First into Human (FIH) studies. We welcome EMA's decision to review and update the pivotal document 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products' (EMA/CHMP/SWP/28367/07). We believe that this revision offers an ideal opportunity to clarify that the purpose of FIH studies is to begin to explore the human pharmacology of the medicine being tested and that safety <u>follows</u> from this knowledge. The TeGenero and Bial studies have both shown the importance of considering human pharmacology in the design of safe FIH studies. The 2007 Guidelines have no overall statement about the purpose of FIH studies. Instead, the introduction discusses issues around safety without clarifying that FIH studies should be designed to test the relevance of pre-clinical pharmacological data to human dosing, comparing it with evolving pharmacokinetic and pharmacodynamic data/knowledge as the study proceeds. A statement that FIH studies are focused on human pharmacology, and not toxicity, will ensure that the studies are designed to study the pharmacological effect of the medicine. Currently, too many studies – like the Bial study - are designed to test the maximum tolerated dose of a medicine, not the pharmacological effect. Since the safety of volunteers in FIH studies is paramount, this should not be acceptable and stated as such in the Guidelines. The Guidelines are a powerful place for making clear statements on these matters that are fundamental to the design of FIH trials.	The revised guideline now defines the purpose of FIH trials as to evaluate an investigational medicinal product (IMP) in humans for the first time, to study the human pharmacology, tolerability and safety of the IMP and to compare how effects seen in non-clinical studies translate into humans.

Stakeholder no.	General comment	Outcome (if applicable)
	We therefore request that the Guidelines state that: • The primary objective of FIH studies is to understand the mechanism and pharmacology of a new medicine in humans • Tolerability and safety should only ever be secondary objectives • The maximum tolerated dose should never be an objective in a FIH study	
31	We hereby would like to draw your attention to the fact that phytomedicines and medicinal products of other traditions, e. g. homeopathy or anthroposophic medicine, are often based on complex compounds such as plant extracts, for instance. Therefore it could be necessary to take into account that for these medicinal products one single active substance with clear preclinical data can only seldom be identified. Consequently, overall risk assessment for FIH and early CT administration as well as translation of non-clinical data to human use by extrapolation on the basis of PK- and PD-data will only in rare cases be possible for these medicinal products. We therefore ask you to consider the special characteristics of phytomedicines and medicinal products out of the scope of chemically synthesised medicinal products based on complex compounds in the revision of this guideline.	The issue is addressed in the scope of the revised guideline which applies to all new chemical and biological IMPs. A statement has been added in the introduction however 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.
33	For centuries, assessments of medical risks almost always began with experiments through surrogate “model” species, whether prokaryote or eukaryote. The cautionary wordings about the transfer of animal test data to humans, found in the Guideline adopted by CHMP on 19/07/2007 (in the wake of the TGN1412 affair) and again in the “Concept paper” for the present revision, leaves the responsibility of the transfer to the team in charge of the clinical trial. In the aftermath of the Rennes disaster, which ones again occurred despite BIA 10-2474 had successfully passed the trial in chimps (the best possible model of humans, if any), this uncertainty must be ironed out. It is the role of EMA to introduce scientific rigor in the whole clinical trial procedure. The goal is to avoid the sacrifice of a volunteer in whatever trial to come, which would lead to the nth guide for FIH trials, and may compel health authorities to complaints of	Limitations of animal models should always be taken into account, when developing new pharmaceuticals. That does not mean that animals models cannot be helpful in reaching a proof-of-concept. A tailored, uncertainty-based approach for each trial is emphasised in the revised guideline, taking all available data into account,

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	non-assistance of endangered humans and manslaughter First, the “model” concept is at odds with a basic, logical principle embedded in the very definition of species on Earth: their reproductive isolation. For vertebrates for instance, this means that only gametes donated by male and female individuals from the same species can recombine and warrant offspring. At the molecular level, the hybridisation process of gametes can only proceed between genomes of similar structures, subjected to similar organisation, control and regulation of gene expression (OCREGENE). Genomes of two different species, even closely relation in evolutionary terms like rats and mice, or humans and non-human great primates, cannot hybridize because of different structure and OCREGENE characteristics, also known as “species barrier”. Upon exposure to the same challenge, each of the two species will react with its own genes and OCREGENE characteristics, the issues in the two might be similar (never identical), different or opposite. This uncertainty can only be lifted after exposure of both species to the same challenge, making any “model” experiment pointless. No species is a reliable biological “model” for any other species. Challenging this statement amounts to negate the existence of the species barrier, which is absurd. Considering valid for humans preclinical result from “model” species amounts to play “Russian roulette” with the life of the human volunteer. The results of preclinical testing must be considered as strictly unreliable for humans. Furthermore, for popular “model” species like rodents, thousands of strains are available allowing selection for –or against- a chosen phenome, which can further seriously bias the result derived from a test performed in a “model”. FIH clinical test disasters, dramatic as they are, are rare because vigilant clinical staffs most often stop the test as it is turning awry. In comparison, adverse side-effects of drugs (ASED) are many times more prevalent. Despite all drugs had successfully passed pre-clinical and clinical trials, ASED claim every year 190.000 lives in the EU alone, proving that both trials are riddled with notorious loopholes. ASED and FIH victims succumb to the same cause: inadequate trials of drugs, a problem which has been lurking for	in a careful manner based on scientific argumentation.

Stakeholder no.	General comment	Outcome (if applicable)
	decades.	
33	When it comes to human health issues, specifically for pre-clinical and clinical tests, it is mandatory to consider as unreliable any result from model experiments. The only valid and reliable biological model for humans are humans, and, to begin with, biological material of human origin (cells, tissues...). Therefore, only science-based results obtained from humans and human-derived materials shall be taken into consideration for pre-clinical and clinical tests. Introduction of a "phase zero clinical test", replacing present-day preclinical tests. All volunteer candidate must accept to participate in non-invasive tests proposed in the recently developed Precision Medicine*. (i) Molecular and cellular investigations (genome sequencing, various "-omics" explorations) in iPS cells donated by each candidate and dedifferentiated into cell lines of interest and even miniorgans. (ii) Systems biology investigation, focussing on the effects in, and interactions of, tissues and organs likely to be most exposed to the drug candidate (hepatocytes, neurons, epithelial cells...). (iii) Examination of the candidate volunteer using various, relevant Medical Imaging methods. These tests must be performed before the cells and tissues of a candidate volunteer are exposed to the drug to be investigated, and again after these materials are exposed to the drug, at various concentrations and for various times. The results of all these tests must be analysed by a competent medical panel, which will establish a dossier for each candidate and make the final selection of the volunteers. The dossiers of the latter will be available to the clinical team throughout the clinical tests. The "Phase Zero" investigations should be performed in a European Scientific Risk Assessment Institute (to be created). The expenses of this investigation should be charged to the enterprise asking for the clinical test. *) See for example "Biomarker Tests for Molecularly Targeted Therapies: Key to Unlocking Precision Medicine" THE Graig, JK Philips & HL Moses EDTS, the National Academies Press, DOI: 10.17226 / 21860 and "Evolution of Translational Omics: Lessons Learned and the Path Forward ", CMMicheel, SJ Nass & GS Omenn EDTS, the National Academies Press, DOI: 10.17226 / 13297, especially the chapter 3, p.65-78." Best Practice for Omics-Based Test Validation Prior to use for Patient Management Decision in a Clinical	The proposed approach is considered outside the scope of the current document.

Stakeholder no.	General comment	Outcome (if applicable)
	Setting ".	
34	The attempt to establish a uniform guideline for all First in Human Studies appears to be at least difficult, as increasingly the classical ascending single dose studies with a kinetic part and a start from NOEL or MABEL are replaced by mechanistic prove of concept studies as first in human studies. In many cases, the so - called "pre - phase I" studies with mechanistic approaches, are the starting point in the humans. In many cases (PET, other imaging or kinetic methods and in some other cases), these mechanistic studies can only be carried out in appropriate patients (eg cytotoxic substances, binding studies or biomarkers) and not in healthy volunteers. Thereby a uniform strategy seems not to be appropriate for all studies and such a guideline is either inappropriate in many cases or too vague to enclose all possible studies. However, overloading of protocols should be avoided as a single, continuous study with 3, 4 or more arms or staggered groups, since no external assessment can be carried out between the individual study parts and the safe prediction over many stages without knowledge of interim results is not sufficiently safe / feasible. The implementation of a Phase I development plan, with a shorter period of approval of 14 days for the individual parts of the study, which is provided for in the German GCP regulation (GCP-V), is too rarely used in our experience (in our ethics committee, not even once in the past 10 years). Since some time sequences should be planned between the individual dosages and groups in order to be able to recognize delayed risks as well, the use of this concept would only cause delays of a few days. Alternatively, it would be conceivable that representatives of the ethics committee and the licensing authority are integrated into DMSB structures and then continuously evaluate the interim results that are emerging and thus follow suitably adapted approval procedures. Overall, the first-man studies of patients in the sense of mechanistic "healing tests" appear to be more appropriate in ethical aspects, since in addition to the risks of a first application in humans, a benefit due to the treatment of the disease is also possible, whereas in healthy volunteers only an increased self-esteem due to the altruism regarding of taking risks for science and society would be possible.	The intention of the guideline is 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. Other issues are considered too specific detail.

Stakeholder no.	General comment	Outcome (if applicable)
	Furthermore patients compared to healthy people (is a 20 year old male non-smoker a model for eg. a 70 year old smoker with NSCLC), might be the more appropriate investigational subjects. Not only the question arises whether if animal experiments are always a reasonable surrogate for Homo sapiens, but also, in some cases, if healthy persons are a suitable surrogate for some groups of patients. Furthermore there might also be different risk constellations for patients and healthy volunteers (would the cytokine storm seen after application of TGN 1412 have been in the same order of magnitude in patients of the targeted patient group as in healthy individuals with a full functional immune system?). An additional point to discuss, in first in human studies, is the question if the differences in the evaluation of α and β errors are appropriate from an ethical point of view. Is a "dead person" due to an false positive tested substance considered "more valuable" than a "dead person" due to a therapy refrained due to false negative results (omission of a possible effective therapy not discovered (false positive and false negative results, "standard" 0.05 and 0.8 [= 0.2])). These assumptions may be appropriate with regard to development risks in pharmaceutical industry (as few futile investments as possible for substances that do not yield a return on investment afterwards in comparison to lost opportunities to earn money that are not real money but "only" lost profit opportunities). However, other standards should be used from an ethical point of view.	
35	The proposed revisions and updates to the "Guideline on strategies to identify and mitigate risks for first-in human clinical trials with investigational medicinal products" are welcome and timely given the recognition that the design and execution of early phase trials has become increasingly complex and challenging in recent years. Clinical Research Units and Contract Research Organisations deliver increasingly complex early phase/FIH trials. Review of protocols before acceptance of a trial should be done with the appropriate level of expertise including statistical, clinical specialist input (e.g. oncology), pharmacy and pharmacological input. Consideration should be given to whether Phase 1 accreditation needs to become mandatory for all units delivering Phase 1/FIH studies.	Sponsor processes prior to submission of a CTA are outside the scope of the guideline. However, the importance of appropriate site facilities and personnel is included.

2. Specific comments on concept paper

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Title	6	Proposed change: Please see suggested changes in red below: Please change title to: Concept paper on the revision of the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products'(EMA/CHMP/SWP/28367/07)	Title is as proposed and not subject to change.
Title	10	Comments: ACRO strongly supports the proposals in lines 35 and 51 – 52 to extend the remit of the guidance beyond single ascending dose first-in-human trials to incorporate other early phase trials and designs. Consequently, ACRO recommends that the title of the revised guideline is changed to reflect its revised scope. Proposed change: Change title to: “Guideline on strategies to identify and mitigate risks for human pharmacology clinical trials with investigational medicinal products”	In line with EMA process, the text of a concept paper per se is not revised in light of comments but the comments are considered in the context of the revision of the actual guideline itself.
24	18	Comment: Please clarify what is meant by “integration of the non-clinical data available before FIH administration”.	Not accepted. Too specific detail.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
24-26	25	Comments: EFPIA supports the update to the guideline as noted, but would like the new guidance to acknowledge that specific CTAs will have gaps relative to the ideal data package (e.g. uncertainties in animal-to-human and In vitro-to-In Vivo translation) and therefore a flexible risk-based approach is probably warranted for each case. The sponsor should discuss preclinical data gaps or uncertainties in the CTA and highlight how such gaps were addressed in CT design and dosing. Proposed changes: The guidance should highlight the scientific aspects and principles to be addressed in a reliable submission, but should also acknowledge that all criteria will not be met on every single compound. The guideline should not be overly prescriptive and leave room for the Sponsor to design early clinical trials based on a thorough risk assessment of the individual compound in development, particularly for indications with unmet medical need or life-threatening or severely debilitating disease, while discussing a risk-based approach in the CTA. The guidance should also mention whether it refers to all first-in-human studies, including small and large molecules, gene, cell and tissue-based therapy, first-in-human studies in healthy volunteers and patients, and/or all type of indications.	A tailored, uncertainty-based approach for each trial is emphasised in the revised guideline, taking all available data into account, in a careful manner based on scientific argumentation.
26-28	6	Proposed change: ... Consequently, the practice has evolved and many FIH trials are now performed with integrated protocols potentially combining a number of different study parts, e.g. single and multiple ascending doses (SAD and MAD),...	Text of the concept paper per se is not revised in light of comments, see above.
32-59	2	Comments: One of the major challenges we face today in this issue is the definition of minimum requirements of pre-clinical for the first clinical trial with biological and biotechnological products. Which is why it is vital that the	The requested approach is covered in the ICH Guidelines ICH M3(R2) and ICH S6 (R1).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		new guide will dedicate a space to this topic Proposed change: refer to the minimum requirements for preclinical first clinical trial	
35	10	Comments: Except for FIH studies, identification and mitigation of risks could be done for any study with an anticipated exposure higher than the previous dose in humans. This includes SAD, MAD as well as studies at a later stage when escalating further than done before.	Comment noted.
35	14	Comment: Extension of the guidance to early phase CTs including single study or integrated protocol designs should be further specified and clarified. Proposed change: This is highly appreciated and creates a framework for the design of first in human (FiH) studies. Additionally, it is suggested that: 1. It will be applicable to both healthy and patients FiH studies. 2. Risk mitigation measures should apply over the whole integrated protocol and these are already included at submission stage in an algorithmic approach (e.g. decision tree for choosing doses). Gaps in this algorithm should be shared with regulatory/ethics committee as data emerges.	A tailored, uncertainty-based approach for each trial is emphasised in the revised guideline, taking all available data into account, in a careful manner based on scientific argumentation.
35	25	Comments: 1. Guidance should recommend when it is appropriate to specify protocol components for the integrated protocol based on nonclinical information (translation or extrapolation) versus allow sufficient flexibility in	A tailored, uncertainty-based approach for each trial is emphasised in the revised guideline, taking

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		protocol design to update components based on accruing PK, PD and safety from the trial itself. 2. Consideration should be made for the differentiation between patient or healthy volunteer studies, dose escalation studies and hybrid studies with expansion cohorts. Specific discussion on when the FIH studies could be healthy volunteers vs affected disease patients. 3. We suggest that the EMA consider how newer strategies such as adaptive design (incorporation of Bayesian models) might support dosing strategies, including dose escalation, since such approaches, when used properly, can reduce necessary numbers of trial participants and may more precisely define maximum doses/exposures. 4. Clarification required on definition of early clinical trial (CT) – does this mean the first study regardless of whether it is a stand-alone or combined study, in which case a stand-alone MAD study would not be included. Some stand-alone biopharm studies may be done “early” but presumably not included here under “early CT”?	all available data into account, in a careful manner based on scientific argumentation.
35, 50-53	5	Comments: Provide guidance on considerations for moving from healthy volunteers to patient populations in a single study (e.g., situations where a dose lower than the MTD in healthy volunteers may be warranted if there are specific concerns about sensitivity in the target population).	This is covered in the updated guideline.
35-44	5	Comments: Describe the agencies' position on Phase 0 studies (e.g., microdose) and how they can be used to guide traditional phase 1 clinical trial design and dosing. In addition, describe the unique safety considerations and required preclinical data. Describe if the preclinical data required for Phase 0 studies differs from Phase 1.	The requested approach is covered by ICH M3(R2) and referred to in the guideline.
36-43	18	Comment: The concept of better integration of pharmaco-PK/PD-Tox data is described. However, there is a tendency to	A tailored, uncertainty-based approach for each

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		focus on mathematical extrapolation of quantitative data without sufficient emphasis on the science-based use of translational safety biomarkers. The concept paper should explicitly recommend the use of safety biomarkers from preclinical pharmacology or toxicology studies in clinical monitoring, where appropriate. Comment: IQ supports the concepts outlined in this section, however, saying 'better integration on non-clinical pharmacology data' is not that meaningful, as there is not a 'one size fits all' approach. Acknowledging and highlighting in dossiers the places where prediction of human effects might be different to preclinical species would be more practical. In Vitro to In Vivo correlations of pharmacology is not always straightforward, for example, and confidence will vary across programs. Understanding the time course of PD effects is important, but in many instances we do not have any measurable PD effects in FIH studies. Also, measuring PD effects in the periphery and its alignment with that in the CNS is another assumption that requires case by case consideration. While IQ is thematically supportive, we wish to acknowledge the uncertainties that will arise and request the necessary flexibility required in the application of such principles to each specific compound and pharmacologic class. Proposed change : Increase verbiage recognising the need for flexibility.	trial is emphasised in the revised guideline, taking all available data into account, in a careful manner based on scientific argumentation.
37-39	5	Comments: Study design and safety monitoring Early clinical development is moving towards early demonstration of proof of principle and appropriate target engagement. This is based on the frequent failure of larger, expensive phase 2 and 3 studies. Phase 1 studies should be designed in a thoughtful manner to determine, whenever possible, not only the PK and safety and tolerability, but also to demonstrate target engagement in humans. This can be done by measuring pharmacodynamic responses or demonstrating appropriate target binding in imaging studies. This	This is covered in the updated guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		will hopefully lead to better decision making for sponsors and reduce the overall costs of the drug development process. The revised guidance document should emphasize this principle.	
37-39	5	Comments: PK-PD modeling and simulation to optimize human dosing Expand on the benefits of PK-PD modeling and simulation to plan early phase studies, particularly related to optimizing efficiency and reducing risks to subjects. The current guidance only mentions dose-response curve and determining PK in vivo with some additional comment on PK-PD modeling to determine the MABEL (p. 7 of current guidance).	PK-PD modelling is included in the revised guideline.
37-39	18	Comment: Reliable, accurate prediction of human PK or PK/PD modelling is challenging and sometimes not possible due to uncertainty of the translatability of preclinical data and the lack of appropriate animal models or relevant PD biomarkers. In such cases Sponsors should provide an estimate of efficacy and this may be based on in silico, in vitro or other information. However, in all instances the Sponsor is responsible for outlining the assumptions made and establishing a clear rationale for their use. Comment: IQ considers that target engagement, half-life of the molecule, target turnover and other PD attributes of the investigational product should be taken into account in the design of the nonclinical safety and clinical studies.	PK-PD modelling is included in the revised guideline.
37-39	25	Comments: Saying 'better integration of non-clinical pharmacology data' is not that meaningful as there is not a 'one size fits all' for this. Acknowledging and highlighting in dossiers places where prediction of human effects might be different to preclinical species would be more practical. Examples: In Vitro-In Vivo correlations of	A tailored, uncertainty-based approach for each trial is emphasised in the revised guideline, taking

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		pharmacology is not always straightforward and confidence will vary across programs. Understanding the time course of PD effects is important, but in some instances we do not have measurable PD effects in FIH studies. Also, measuring PD effects in a surrogate location (e.g. the periphery for a CNS indication) is another assumption that requires case by case consideration. Proposed changes: The guidance should explain what is meant by 'better integration of non-clinical pharmacology data'. Please acknowledge that uncertainties extrapolating from preclinical pharmacology and toxicology data to humans will arise. Additionally, appropriate animal pharmacology models are often not available and human genetics data should suffice. While nonclinical PD models may be useful to demonstrate a PD effect, the nonclinical PD response is often not relevant to a clinical PD response and human genetics data may be more relevant. Please include that sponsors can address the key principles of "better integration" (when clarified) in the IB/CTA, but have flexibility to discuss any uncertainties in the application by integrating all in silico, in vitro and in vivo pharmacology, pharmacokinetic and toxicology data into an overall risk assessment.	all available data into account, in a careful manner based on scientific argumentation.
37-39	25	Comments: We suggest that EMA include a discussion about how prior nonclinical and clinical data and knowledge around target biology can suggest on-target class effects and therefore might influence FIH study designs and safety monitoring. Proposed changes: Clarify what non-clinical and clinical information is desired in SAD/MAD designs and IB/CTA for known pharmacologic classes. Note that access to data from competitors of the same pharmacologic class is limited (not in the public domain) and make some allowance for this.	It is stated in the guideline that experience with molecules having a similar mode of action can be useful when designing an early CT. Access to data is outside the scope of the current guideline.
37-	25	Comments:	The revised guideline addresses selectivity but

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
39		Pharmacology profiling across preclinical species and humans should be conducted. Proposed changes: for In vitro selectivity testing: 1) define the minimum multiples of primary pharmacology that should be tested, while recognizing that due to solubility limits these may not always be achievable. 2) Include an assessment of relevance to the human situation depending on format of the test, especially human versus animal, is it a functional test or not and relative to known target distribution.	more detail is too specific.
37-39, 48	5	Comments: Provide stronger guidance on the use of animal toxicology data for risk assessment in humans and safety monitoring in FIH studies.	Detailed guidance on the use of animal toxicology data is provided in the revised guideline.
37-41	25	Comments: Sponsor should specify whether or not the test article is pharmacologically active in the species used for toxicology testing and describe potency comparability to humans. Where appropriate and feasible, biomarkers of pharmacologic activity may be included in the toxicology studies. This information may provide important human safety perspective around adverse findings observed at high doses in animals. Proposed changes: Clarify in section 'Relevance of animal species and models' to what extent pharmacological activity in toxicology species should be characterized and described in the CTA to consider a toxicology species relevant.	Detailed guidance on the use of animal toxicology data is provided in the revised guideline
37-47	25	Comments: The use of non-clinical data for the estimation of a therapeutic exposure is only an estimate. Translation is	A tailored, uncertainty-based approach for each trial is emphasised in the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		not always predicted. Preclinical data represent part of the dataset that inform actual dosing in SAD/MAD. Proposed changes: Acknowledge that preclinical data represent estimates of PK/PD and safety features and include that emerging clinical data in SAD/MAD trials using a risk-based, totality of evidence approach will inform dose escalations, dose frequency, dose interval determinations, and the justification of the top exposure.	revised guideline, taking all available data into account, in a careful manner based on scientific argumentation.
40	18	Comment: Please explain further what the Agency means when its states “verification of assumptions made”. If this implies that effects seen in an animal model are verified as to translatability to humans, then this may not be attainable without the ultimate human study. Otherwise, this line should be further clarified as to the expectations. Comment: Verification of assumptions about translatability of nonclinical data is not really possible prior to FIH; testing assumptions made for nonclinical data depends on analysis of human data, and is therefore retrospective. Thus, assessing the translatability of a nonclinical model is inherently retrospective. This presents challenges for novel targets. We must acknowledge that certain assumptions always underlie nonclinical data and that nonclinical data may not translate to humans. On the other hand, it is desirable to clearly articulate the assumptions that underlie any predictions about translatability (i.e. target or off-target potency, metabolism, transporter effects, etc). In addition, please provide clarity around how assumptions are tested and subsequently used. Comment: Depending on the novelty of the target or treatment, the verification of assumptions may be impossible.	Verification of assumptions relates to the use of emerging clinical data which is dealt with in the guidance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: ...and verification of assumptions made whenever possible prior to the FIH CT or how data generated in the early CT will be used to check assumptions i.e., via a decision tree. In addition, it is desirable to clearly articulate the assumptions that underlie any predictions about translatability (i.e. target or off-target potency, metabolism, transporter effects, etc.)	
40-41	25	Comments: “verification of assumptions” is broad and difficult to know what it means. Also, not all assumptions will be able to be verified. If the goal of using preclinical information is to design and conduct clinical trials that permit the safe characterization of human pharmacology, safety and tolerability, then please clarify what assumptions need to be verified to support this goal. Proposed changes: Clarify what “verification of assumptions” means and what verifications are critical to the key goals of SAD and MAD trials.	Verification of assumptions relates to the use of emerging clinical data which is dealt with in the guidance.
40-41	25	Comments: Reliable, accurate prediction of human PK or PK/PD modelling is challenging and sometimes not possible due to uncertainty of the translatability of preclinical data and the lack of appropriate animal models or relevant PD biomarkers. Proposed changes: Please acknowledge in the revised guidance that in the absence of relevant clinical PD biomarkers, minimal targeted exposures should be related back to relevant multiples of in vitro potency and adjusted for other important variables such as plasma protein binding. Also, knowledge of in vitro potency across species	Use of PK/PD modelling is included in the revised guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(mainly in pharmacological model and in human) is important.	
40-45	5	Comments: Calculation of first dose in man and dose escalation Provide more explicit guidance on how to determine the first dose in man. 1. Detail the calculation of the No Observed Adverse Effect Level (NOAEL) 2. Detail the calculation of Minimal Anticipated Biological Effect Level (MABEL) 3. Provide a general guidance statement for the safety factor to be used 4. How to determine the most appropriate preclinical animal model	Issue of dosing is addressed in detail in the revised guideline.
40-47	25	Comments: The guidance should address stopping criteria when translatable biomarkers for pharmacology are weak or not feasible. And, updates to the guidance should acknowledge and provide recommendations for situations in which nonclinical safety and/or pharmacology data may be limited or misleading for use in stopping criteria. A clinical MTD in this instance may be a primary stopping criterion. Most programs have safely reached MTD in the clinic and future guidance should not limit ability to define MTD. Proposed changes: High quality translatable biomarkers may not always be available for human SAD or MAD studies and the translatability of on- or off-target safety findings may be difficult to define during initial stages of clinical development. In such cases, it may not be possible to conclusively identify target efficacious clinical exposure levels and a clinical MTD in this instance may be a primary stopping criteria.	Stopping criteria are extensively addressed in the revised guideline.
40-	25	Comments:	This is referred to in

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
47		Before the translatability of nonclinical models to humans can be considered, sufficient nonclinical quantitative data should be generated to explore the reproducibility and exposure-effect relationship (i.e. by modelling and simulation) using the compound in question (i.e., preferably no analog). This information, in addition to, where possible, human genetic data and relevant clinical PD biomarkers should be used to inform the clinical dosing strategy – both the starting dose as well as the dose escalation. These relationships should be expanded to include an analysis of the TK/TD. Where available, these quantitative relationships could be used to identify a dose above which no further benefit is likely. Proposed changes: Revised guidance should describe the desired characterization of preclinical PK/PD translation and its relation to human starting exposures, escalation intervals and maximum exposures – even after a maximum PD effect is observed. Please recognize in the guidance that uncertainties will arise with any dataset and permit the necessary flexibility within the clinical trial conduct to use the data in an integrated manner. In addition, because of limitations of translatability of 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.	general terms, as more detailed guidance is too specific. Use of all data in an integrated manner is emphasised. Reference to exploratory clinical trials is included in the revised guideline.
42	14	Comments: Only MABEL mentioned as approach. Proposed change: It is suggested to consider aligning with other safe starting dose calculations or recommendations based on no observed adverse events level (NOAEL) and pharmacologically active dose (PAD) as per 2005 FDA Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers Guidance.	The revised guideline contains a section on dosing which takes this approach into consideration.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
42	18	Comment: IQ asks that the Agency provide clarity regarding how to implement a MABEL approach expanding to “all biological effects” without resulting in an overly conservative starting dose that unnecessarily slows down drug development progression. Hence the appropriateness of this proposal needs further consideration and dialogue. In addition, we note that the existing wording in 2007 guideline on the calculation and use of MABEL is already very comprehensive. Comment: IQ considers that the application of MABEL to CTs, for which a risk assessment demonstrates that its use is unwarranted, will be extremely detrimental to clinical research and would not provide additional benefits from a clinical safety perspective. Comment: The proposed revision should clarify the conditions where MABEL is recommended, whatever is the drug format (small or large molecules) and also further clarify the type of risk factors triggering a MABEL strategy as compared to a NOAEL or others, with flexibility for scientific judgement.	The revised guideline contains a section on dosing which takes this approach into consideration.
42-43	25	Comments: Expanding MABEL approach should be discussed in line with risk factors which should be redefined. Proposed changes: Calculation should be detailed both for MABEL approach and for NOAEL approach. For NOAEL approach, recommendation should be provided if the most sensitive animal species differs from the most relevant animal species.	The revised guideline contains a section on dosing which takes this approach into consideration.
42-	25	Comments:	The revised guideline

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
43		Preclinical data should define a minimally active dose when feasible to guide the starting dose in SAD and MAD. Not all preclinical changes should be weighted equally and the focus should be with meaningful changes rather than spurious or minor effects. See proposed changes for factors to include. Proposed changes: The impact of the nonclinical MABEL and/or NOAEL on SAD/MAD starting dose should take into consideration cross species potency differences, PK access to target tissue, and other PK drivers such as plasma protein binding. Endpoints should focus on meaningful biological effects for risk assessment and not minor or spurious changes that are changes not considered meaningful to the risk assessment (e.g. effects known to be unique to specific species). The guidance should not be overly restrictive on starting doses and flexibility should be granted for trials in patients in diseases with high unmet need, relative to a MABEL approach that may be considered for healthy volunteers in SAD/MAD when feasible. In cases where a PD biomarker is unavailable and the MABEL cannot be readily defined (due to limitations in methods to assess intended pharmacology in animals or humans), the starting dose should be based on the NOAEL from nonclinical toxicology studies, with appropriate considerations for dose escalation and safety monitoring based on the entire nonclinical data package.	contains a section on dosing which takes this approach into consideration.
42-47	25	Comments: Please clarify what minimum key data describes “taking all biological effects into account” and what data is not considered important for deriving MABEL, escalation steps and stopping exposures. See proposed changes for specific recommendations. Proposed changes: Maximum exposure level in SAD/MAD should take into account interspecies differences in unbound fraction for small molecules, target binding, pharmacology, CNS penetration, and whether the toxicity defined non-clinically is clinically relevant, monitorable and reversible or not. Starting doses should also take into	The revised guideline contains a section on dosing which takes this approach into consideration.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		account species differences in efficacious concentrations. Escalation steps and maximal exposures will also rely on emerging clinical data. Starting dose, maximum exposures and escalation steps should use PK/PD modeling when it's reliable and has utility - recognizing that in some instances good models will not be available and other criteria will be used. Thus, expanding on the minimum anticipated biological effect level (MABEL) approach should focus on taking all relevant biological effects into account.	
44-48	10	Comments: Inclusions of the items on lines 44-48 in the guidelines would be of great value. Proposed change: ACRO suggests “estimated therapeutic exposure, maximum human exposure level” instead of “estimated therapeutic dose, maximum human dose level”.	The revised guideline includes a statement that whenever dose is mentioned, the expected exposure at that dose should always be taken into consideration.
44-48	14	Comments: Role of non-clinical data Proposed change : 1. Interpretation of non-clinical data in IB and/or protocol, not only presentation of data 2. Maximum human dose level (both for SAD and MAD parts) should be critically discussed and the purpose of escalating up to the maximum tolerated dose should be re-evaluated. 3. The presence or absence of adverse events in animals should be critically discussed in light of animal physiology in the relevant species.	These issues are addressed in the section on non-clinical aspects.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		4. Relevance of adverse events due to extreme conditions in toxicology studies should be discussed. 5. Key non-clinical information to be included in a trial protocol: a. Accumulation b. Metabolism differences between species c. Protein binding d. Secondary PD	
45-46	18	Comments: Nonclinical data may be used to estimate a futility dose, above which additional dosing is not anticipated to provide benefit in subsequent studies and off-target effects become more likely. However, such estimations of futility doses (based, for example, on receptor occupancy at the site of action) are frequently limited by uncertain translatability of animal models to humans, and healthy volunteers to patients. Proposed changes: Please consider: “estimated therapeutic dose, estimated maximum human exposure level (both for SAD and MAD parts), dose escalation steps and dosing frequency and intervals;” Comment: It is true that non-clinical data has an impact on dose escalation steps, dosing interval and dosing frequency, but PKPD modelling will play a role here also. When the highest targeted therapeutic exposures and/or maximum PD effect have been achieved in SAD and/or MAD, modestly higher exposures may be explored in the FIH to provide safety data at a higher margin of exposure. Such data are helpful as compounds are advanced in development into bigger and	The revised guideline contains a detailed section on dosing.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		longer trials to account for normal patient variability, as well as to support higher exposures in a TQT study or in the setting of special populations or DDIs. Because often we don't have quantitative translatable biomarkers (i.e. unclear translation between biomarker to disease endpoints) in FIH studies, this permits additional data to bridge such disconnects. Also, in some cases higher doses are needed to demonstrate that PD plateau is achieved. The PD endpoint needs to be relevant for the disease under study, recognizing that what we can measure (e.g. in plasma) may not necessarily represent the site of action for efficacy.	
45-46	25	Comments: Nonclinical data may be used to estimate a maximal dose, above which additional dosing is not anticipated to provide benefit in subsequent studies and off-target effects become more likely. However, such estimations of maximal doses (based, for example, on receptor occupancy at the site of action) are frequently limited by uncertain translatability of animal models to humans, and healthy volunteers to patients. Proposed changes: Please consider: <i>estimated therapeutic exposure, estimated maximum human exposure level (both for SAD and MAD parts), escalation steps and dose frequency and intervals;</i> and permit allowances for such uncertainties in starting and stopping exposures/doses.	The revised guideline contains a detailed section on dosing.
45-46	25	Comments: A risk-based, totality of evidence approach should be applied to dose escalation, dose frequency, dose interval determinations, and the justification of the top dose. Establishing a top clinical dose should be guided by exposures and not dose, pharmacodynamic endpoints up to the maximum pharmacologic effect, human MTD and the exposure limit set by toxicity studies. Emerging clinical data may modify the above. Proposed change: Please include these concepts into the revised guidance.	The revised guideline contains a detailed section on dosing.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
45-46	25	Comments: Please include text in the revised guidance that addresses how much higher exposures should be extended after a maximum PD effect has been reached in SAD/MAD with no MTD and toxicology coverage supports much higher exposures. See proposed comments for specific recommendations that justify exploring higher exposures for what are routine considerations (PK variation, TQT doses and DDI) during development. SAD/MAD studies are the safest setting to explore them. Proposed changes: When the highest targeted exposures and maximum PD effect have been achieved in SAD and/or MAD, then higher exposures may be explored provided toxicology limits permit. PD endpoint(s) should be “relevant” for the disease under study, with consideration for potential differences between peripheral compartments and the site of action for efficacy, and/or differences in species pharmacology. If there is confidence that the PD effect has been saturated at the site of action in humans, scientific justification should be provided for exploring higher exposures and how far above the maximum PD effect is reasonable.	The revised guideline contains a detailed section on dosing.
45-46, 58	5	Comments: Provide more explicit guidance on how to determine the maximum duration of dosing in multiple ascending dose studies.	The revised guideline contains a detailed section on dosing.
45-47	18	Comment: We would propose that “maximum dose level” should be replaced with “maximum exposure”. Comment: Nonclinical studies cannot “define” stopping criteria. Proposed Changes:	The revised guideline includes a statement that whenever dose is mentioned, the expected exposure at that dose should always be taken into consideration.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Please consider either: “definition inform stopping criteria for the trial;” OR “definition guide the establishment of stopping criteria for the trial;”	
45-48, 51-52, 54-55, 57-58	5	Comments: Provide specific recommendations for study procedures that enhance subject safety. For example, comment on the use of sentinel subjects and staggering dose times.	More detailed guidance on subject safety is included in the revised guideline.
45-48, 51-52, 54-55, 57-58	5	Comments: Provide more explicit guidance on the safety data that should be collected during FIH and other phase 1 studies and the process for reviewing that data in the context of dose escalation.	This is covered in the updated guideline in the adverse events / reactions section.
47	10	Comments: ACRO suggests that the guideline specify identification of the need for an exposure limit for C_{max} and/or AUC depending on significant tox or highest exposure in animal studies. In addition to “estimation of the first dose in human,” the guideline could use a section on “determination of the max acceptable dose in human”.	The revised guideline contains a detailed section on dosing.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		ACRO suggests that the guideline specify that not all stopping criteria can be carved in stone - tolerability depends on duration and reversibility, as well as severity. Therefore the Investigator should always have the discretion to stop escalation.	
47	25	Comments: Please clarify what non-clinical considerations will constitute “definition of stopping criteria for the trial”. Nonclinical data alone cannot “define” stopping criteria as these are contained in the clinical protocols and have a wide array of different considerations from an integrated risk assessment that includes emerging clinical data (e.g. clinical intolerability). Therefore, non-clinical information is a subset of information that contributes to stopping criteria. For example, the NOAEL exposure in the most relevant species can constitute a PK-based stopping limit, but there are also cases where NOAEL exposures may be exceeded, based on emerging clinical safety data and depending on the nature of the safety findings in animals. Thus, stopping criteria are informed by non-clinical 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. Thus, an a priori algorithmic approach to driving stopping criteria that is overweighted by non-clinical considerations or excludes the importance of emerging clinical data is not favored. In addition, preclinical data may have a limited role in defining clinical trial stopping rules, as it may not be clear how well the animal data can predict human responses. Consequently, premature termination of clinical dose escalation based on preclinical data and failure to identify an MTD may increase risk that subjects are treated in subsequent clinical studies with sub-therapeutic dose levels. This risk can be particularly important for subjects with serious or life-threatening diseases with no alternative treatments available. Accordingly, stopping rules should be typically defined based on emerging clinical data, such as frequency of adverse events and observed toxicities and might differ between indications. In some occasions, stopping rules may be defined based on clinical PK and/or PD findings. For example, in cases where further dose escalation is not expected to result in exposure increase due to reaching a PK plateau, escalation to an MTD	The revised guideline contains a detailed section on dosing.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		may not be required. In these specific occasions, where a steep dose/response curve is expected or a long compound half-life with subsequent increased time to steady state is observed, a staggering approach of including patients within a cohort can allow monitoring of adverse events and mitigate risks for subjects included in the clinical study, without compromising further dose investigation and achievement of a therapeutic dose level. Proposed Changes: Non-clinical data constitute part of the dataset that inform stopping limits in clinical trials, which include the nature of the target organ toxicity (monitorable, manageable, and reversible or non-monitorable and serious), NOAEL exposures and human relevance of the target organs observed. In some cases, NOAEL exposures may be justified to be safely exceeded in clinical trials without serious or non-monitorable toxicity. Additional information beyond non-clinical should be considered in formulating clinical stopping criteria and include risk/benefit, PK/PD relationships and confidence and data that emerge during SAD/MAD - clinical safety data, manageability/tolerability of AE's, actual PK/PD relationships and observed PK variation. Thus, clinical trial stopping criteria arise from an integrated risk assessment approach that takes into account the totality of data, for which non-clinical data is a subset and includes emerging clinical data that is not available or predicted at the time of CTA submission.	
47	25	Comments: Mean exposures are appropriate for clinical exposure caps and absolute caps for all subjects would be the exception. Proposed changes: Please acknowledge in revised guidance that mean exposures are the routine metric for starting and stopping exposures for clinical trials and that the exception of an absolute stopping exposure for all subjects is warranted when safety concerns are unusually high – e.g. toxicology data indicates serious, non-monitorable	Not accepted. This was considered but the final guidance states that a dose stopping criterion comprising a maximum clinical exposure (C _{max} or AUC) should generally be included. When reviewing emerging data in relation

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		toxicity and human PK variation is expected to be high.	to this criterion, the maximum exposure observed in individual subjects within a cohort rather than the mean exposure should be taken into account.
48	10	Comments: The bulleted item on line 48 regarding the “identification of safety aspects to monitor” is a very good point, which ACRO strongly supports. Safety assessments should cover vital organs as well as being tailored to detect anticipated risks.	This is addressed in the revised guideline.
48	18	Comment: Although there is mention of the need for integration of nonclinical data in an overall risk assessment (lines 37-39), the use of nonclinical data for “identification of safety aspects to monitor” should include an assessment of potential human relevance of animal findings and translation of nonclinical biomarkers.	This is addressed in the revised guideline.
50	25	Comment: Overlapping cohorts is not explicitly mentioned in the concept paper, but the TSSC report discussed it and it probably needs some discussion/consideration as to when it should be applied. A balance needs to be struck between generating sufficient safety and other data for progression to the next cohort versus completion of dosing and availability of all data prior to progression. A “weight of evidence” approach is suggested where steady state PK levels are achieved, safety data (labs, AEs) are available up to and during steady state and these data are available for the majority of subjects. Start of MAD before full completion of SAD should be allowable, once a sufficient human safety margin, likely via PK assessment, has been reached in SAD phase.	The revised guideline states that overlap of SAD and MAD parts may be acceptable. However, any overlap should be scientifically justified and supported by decision points and a review of available data before

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		For PK information for dose escalation decisions, see above. - Universal requirement to complete full SAD phase before initiating any MAD cohort may place in some cases subjects at greater risk compared to having experience with multiple dosing at lower doses before exposing subjects to higher SAD doses. The wording in protocols should be sufficiently flexible to respond to emerging data without the need for an amendment, potentially with a decision tree used to guide the trial's progress.	starting the MAD part.
50	25	Comment: 1. In general, we would like to see some acknowledgement that the novelty of the mechanism of action (MoA) and the specific properties of the drug should be taken into account rather than a "one size fits all" approach. Particularly important if the guidance intends to cover examples of when an integrated protocol is not acceptable etc. 2. Guidelines should address meaningful sample size of expansion cohorts, maximal number of expansion cohorts, handling of combination expansions with SOC 3. The EMA should consider guidance on the use of hybrid early phase 1 trials with expansion cohorts.	A tailored, uncertainty-based approach for each trial is emphasised in the revised guideline, taking all available data into account, in a careful manner based on scientific argumentation.
50		Comment: 1. A risk-based, totality of evidence approach should also be taken to determine dose escalation and magnitude of escalation for each escalating cohort. There is generally an inherent safety factor built into first doses (based on a margin below MABEL and/or the NOAEL) and the magnitude of subsequent dose escalations should be determined based on the totality of data available for the molecule rather than pre-defined without any consideration for the molecule itself. Further, small steps in dose escalation (<i>i.e.</i> <2 fold) may not lead to meaningful differences in PK among cohorts, yielding unnecessary exposure in patients or volunteers without a gain in knowledge of dose/exposure response. Lastly, it may be	The revised guideline contains a section on dosing.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		appropriate to consider different escalation steps based on the class of compounds (e.g. biologics vs small molecules). Proposed guidance language: Geometric progression in dose escalation (where dose escalation between cohorts increase by a fixed multiplicative factor) is generally appropriate as the large majority of dose-response (concentration/ exposure – response) relationships, whether safety or efficacy, have been shown to be logarithmic in nature. This is due to the characteristics of receptor/ ligand, antigen/ antibody, etc. relationships. That being said, there still may be portions of the dose- response curve which are steeper and should be explored with caution. Further, as the potential concentrations/ exposures in the subjects/ patients approach a margin of safety (MOS) of 1, a more cautious approach to dose escalation may be employed. It should be pointed out, however, that not all FIM studies chose doses high enough to potentially eclipse the MOS. Therefore, it should not be mandatory to abandon the geometric progression of dose escalation at the higher doses in all FIM studies.	
50	27	Comment: Health Authority requests have been received on Novartis FIH CTA submissions after the Biotrial incident to 1) apply sentinel dosing, 2) to apply a more conservative dose escalation in SAD, 3) to provide data from one part of the study prior to initiation of a subsequent part e.g. SAD prior to MAD or Dose escalation prior to dose expansion in the oncology setting, and 4) to have results on PK/PD available prior to dose escalation. We have discussed these aspects and formulated our position below. We hope the EMA concurs with the below in drafting the guideline, in order to keep EU a competitive space to conduct early clinical development: Sentinel dosing should remain a risk-based, case-by-case decision - For molecules with known MOA, and/or not considered as high risk, sentinel dosing should be optional.	The need for sentinel dosing is detailed in the revised guideline taking account of comments received.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		- If warranted, sentinel dosing should be limited to the SAD phase, unless emerging clinical data would suggest the need for a more cautious approach in MAD Provide data from SAD prior to MAD (or from one study part to allow a subsequent part of the study to continue,) - See comment to line 55 regarding the suggestion for rolling review Dose escalation in SAD parts of FIH studies: Novartis agrees with the suggestions to generally start with 3-fold increases in particular for programs starting at MABEL and, if appropriate, gradually move to 2-fold increases for higher dose levels in SAD designs. - Such decreases in the dose escalation scheme may not be required if an exaggerated PD does not pose a risk, if there is no evidence of non-linear PK, and if the class is well understood. - The dose for the next cohort is always reviewed at the dose escalation meeting (study team members including also the external investigator), and our protocols include flexibility to repeat at same dose level or select a lower increase than planned driven by the results from previous cohorts - It would be helpful if differences between small molecules and biologicals are addressed due to the general lack of off-target effects of many biologicals. Requests for PK and/or PD results of the completed cohort before the next cohort: PD: NVS assesses PD during the FIH study, but generally PD effects are not necessary for dose escalation decisions, unless exaggerated PD might be potentially associated with a safety concern. The risks with exaggerated PD should be reviewed on a case-by-case basis. PK: For the majority of cases, non-clinical PK models are appropriate to predict correlative human PK	

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		response. We agree that PK should be measured, but real time PK analyses in between dose levels should be limited to situations where exaggerated PD poses a potential risk, or where there is a narrow therapeutic margin. In addition, the biopharmaceutics drug disposition classification of the compound (i.e. its solubility/permeability) should be taken into account here, as well as the differences between small molecules vs biologicals with longer half-lives. For most programs, PK assessments at periodic time-points will be sufficient as a means to confirm the full PK profile.	
51	25	Comments: Pushing the maximal dose beyond exposure of NOAEL based on simple allometry may be necessary for a number of reasons: 1. To define the safe and tolerated dose range for later phase studies a. Phase 1 trials are conducted with more intensive safety monitoring than phase 2/3 trials in smaller number of subjects: protects large number of patients from safety risks of high incidence rate b. Phase 1 trials should cover exposure variability in large, diverse patient population due to genetics, DDI, hepatic / renal impairment, elderly, and over dose c. Establish supra-therapeutic dose for QT assessment. 2. To define PK/PD relationship that narrows down dose range for later phase trials a. Minimize number of patients exposed to ineffective dose, or potentially unsafe dose b. Achieving or approaching E_{max} is required to define PK/PD relationship c. Allowing multiples over maximal PD effect dose may be required also to account for differences between animal models, or differences in PK/PD relationship between PD marker and efficacy.	The revised guideline contains a section on dosing.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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 finding, 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.	
51	25	Comments: 1. If the updated guidance is to cover study components beyond single-ascending first-time-in-human study, sufficient flexibility should be allowed in the protocol for adjustments (dose, dosing regimen and PK or PD sampling schemes) based on accruing human data from the single-ascending dose study, especially if these design elements were initially designed based on nonclinical data with expected translational uncertainty. 2. Extension of the guidance should differentiate designs of early phase studies in the context of the nature of the compound (as SMOL, cellular) and the medical need in respective indications under investigation (as serious or life threatening diseases with no alternative treatments available or rare diseases). In several such occasions, subjects included in early phase studies are already advanced stage patients where an individual patient benefit and achievement of an optimal therapeutic dose level for subsequent clinical studies should be weighted in the risk/benefit assessment. In the occasions of life threatening diseases, inclusion of design elements in the Phase 1 program that may foster faster overall development should also be enabled by the revised guidance.	This is addressed in the scope of the revised guideline. Some of the specifics of the comment were too detailed to address in the general guideline.

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51	25	Comments: Many of the available neuropsychological exams and cognitive tests have significant variability even within the target patient population and are not valid for healthy volunteers or for screening. Either way, it is appropriate to carefully evaluate these factors along with a risk-based assessment to make the decision as to their inclusion in the clinical trial. Certainly appropriate neurological monitoring in FIM trials continues to be recommended based on the mechanism of action of the drug, if there is likely to be a large signal. We do not recommended that neuropsychological exams and cognitive tests be compulsory for screening and as monitoring for safety endpoints for any agent with central nervous system (CNS) tropism. It is also unclear how incorporation of neuropsychological test batteries would be leveraged to support safety evaluation in a reliable manner and we could see a lot of noise and a lot of false positives using such tools. The neuropsychological exam and cognitive tests would require validation to support their use as either a screening tool or as an early signal of more catastrophic neurological toxicity in phase 1 studies.	This is addressed in the scope of the revised guideline. Some of the specifics of the comment were too detailed to address in the general guideline.
51-52	6	Proposed change: extension of the remit of the guidance beyond single ascending dose FIH trials to incorporate incorporate other early phase trials and designs...	Editorial change.
51-52	7	Comments: the extension of the guidance to incorporate other early phase trials and designs should be excluded or limited to obtaining pharmacokinetic and pharmacodynamic data	Not agreed. This is addressed in the scope of the revised guideline.
52	25	Comment: The guidance should clearly define what is meant by “early phase trials”. The intent of the guideline should be clear, focusing on pharmacology and translational medicine type trials, as opposed to, e.g., relative BA formulation selection/optimization studies, food effect Drug Drug Interaction (DDI) etc.	This is addressed in the scope of the revised guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
53	18	Comment: Please expand on what is meant by “clarification on the choice of trial subjects” as it is unclear. Selection of trial subjects is context specific and it is the Sponsors responsibility to define the patient population. Proposed change: Please consider: “clarification on the choice of trial subjects;, in consideration of the overall expected benefit-risk profile, target expression in different groups of trial participants, and other relevant factors” Recommend recognition that the inclusion of subjects is dependent on informed consent in addition to inclusion criteria as required by the clinical protocol.	Choice of subjects is addressed in the revised guideline.
53	25	Comment: 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 tox 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 tox findings are not monitorable, irreversible and potentially life-threatening: in such cases, PK may be the only surrogate marker 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	Choice of subjects is addressed in the revised guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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 Emax is approaching.	
53	26	Comment: It should be specified that attention should be paid to appropriate incentives Proposed change: "clarification on the choice of trial subjects including attention to appropriate incentives"	This is considered outside the scope of the current scientific guideline.
53	35	Comment: Choice of trial subjects essential: if this includes frail elderly and the very young how should the trial design be adapted? Clear guidance about differences between FIH for patients e.g. cancer and phase 1 with volunteers need to be considered Proposed change: Clear categories of volunteer with justification	Choice of subjects is addressed in the revised guideline.
54	5	Comments:	This is addressed in the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Provide more explicit guidance on study stopping criteria.	revised guideline.
54	10	Comments: FIH trials by their nature are likely to surface events which were entirely unanticipated, and so an option to suspend trials temporarily to enable review of emerging data should be a standard requirement within protocols. Proposed change: The current text which reads “overall dose/exposure range and scheme including stopping rules” should be modified to read “overall dose/exposure range and scheme including stopping and suspension/review rules.”	Stopping criteria including temporary halts are addressed in the revised guideline.
54	18	Comment: Provide clarity regarding when an exposure range and scheme including stopping rules is of value and feasible. For example, locally delivered therapies often cannot characterize in a robust fashion local exposures although systemic exposures may still bring value. Comment: Please consider that the stopping criteria may be different for different trial populations, i.e., rules for healthy subjects might be different from those for patients. Proposed changes: Please consider: “overall dose/exposure range and scheme including stopping rules; which may differ for healthy subjects vs patients”	A tailored approach for each case is emphasised, taking all available data into account, in a careful manner based on scientific argumentation.
54	25	Comments:	A tailored approach for

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		1. For compounds with the same MoA where safety and efficacy have been shown in Ph2 and/or Ph3 studies by competitors, it would be ideal if the guidance provides clarification on what circumstances the competitor data could be utilized to support the development program of the newer compound. This could include starting dose (can a higher dose higher than MABEL be considered) in FIH studies, and necessity for SAD and/or MAD studies prior to Phase 2. 2. A risk-based, totality of evidence approach should also be taken to determine dose and frequency for each escalating cohort. There is generally an inherent safety factor built into first doses (based a margin below MABEL and/or the NOAEL) and the magnitude of subsequent dose escalations should be determined based on the totality of data available for the molecule rather than pre-defined without any consideration for the molecule itself. Again, a totality of evidence approach should be utilized and the rationale for dose escalation magnitude(s) justified. 3. Provide more detailed guidance on how much adult exposure data for safety information is needed for initiation of paediatric studies (structure to frame objective assessment, perhaps algorithmic approach).	each case is emphasised, taking all available data into account, in a careful manner based on scientific argumentation.
54	27	Comment: We have also seen increased requests from Health Authorities questioning the anticipated maximal dose in our first in human designs. While we agree the purpose of the study is not to expose healthy subjects to an unsafe dose, the general principle should be to establish a safety window in the FIH study that takes into account variability of PK in the target population. It is also important to consider that for oncology drugs, the main goal of the dose escalation part of FIH studies is to establish a Maximum Tolerated Dose (MTD)/Recommended Phase II dose, which cannot be predicted from non-clinical data, thus precluding a maximal dose for the trial to be defined a priori in the study protocol.	The revised guideline contains a section on dosing.
54-58	35	Comment: Consideration needs to be given to how doses will be chosen and escalated-how preclinical data and	The revised guideline contains a section on

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		toxicological data will be used, limitations of NOAEL/MABEL, information on drug and target interactions and how individual pharmacokinetic data and data emerging during the trial might guide sequential dosing. Proposed change: Dosing considered in more detail and clear justification for the different approaches used.	dosing.
55	14	Comment: The rolling review of emerging human data during the study is very important and should be further specified in the new guideline. Proposed change : 1. A comparison of emerging clinical data to relevant preclinical data and models should be part of the rolling analysis and accordingly discussed. 2. Safety review committee composition should be defined and when agency/ethics are to be involved via an amendment (e.g. gap in the algorithm or if thresholds from predicted outcome were reached). 3. Clear definition which human data are to be continuously reviewed (e.g. relevant PK for each cohort in a dose escalation design, PD data).	A tailored approach for each case is emphasised, taking all available data into account, in a careful manner based on scientific argumentation.
55	18	Comment: Rolling review of emerging human data should be a best practice in FIH studies, but consideration should be given to the time required to generate data, especially biomarker/pharmacology data. Current industry best practice is to review PK and safety data prior to next dose. However, it is acknowledged there should be flexibility in the availability of PK for each dose escalation, particularly for initial cohorts when the SAD is initiated at very low doses or for the MAD escalation when steady-state PK is predictable from single-doses.	A tailored approach for each case is emphasised, taking all available data into account, in a careful manner based on scientific argumentation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
55	25	Comments: 1. Dose and dosing regimen decisions should be sufficiently adaptive on accruing pharmacokinetic data in early clinical trials. Of note, the initial few cohorts in FIH study are given low doses with very high margin of safety. For these low dose cohorts in FIH study, a frequent cohort-by-cohort review of PK data may be unnecessary in order to safeguard the safety of subjects enrolled. In addition, pharmacokinetic characterization in the early learning phase of drug development is best performed when there are multiple dose levels (especially at dose levels sufficiently above the limit of quantification) or when sufficient numbers of repeated doses have been administered to support a dose decision. Data from 2 to 3 lower doses, with time and dose-linearity sufficiently informed and justified by nonclinical data, should be sufficient to project expectations at higher doses. Rolling review at greater frequency with limited sample size, has high likelihood of leading to erroneous recommendations. The integration of PK/PD data in these escalation decisions should be risk-based. 2. Rolling review of data during the study – we would like to see this allowing for molecule-specific driven approaches with the primary focus on the emerging safety data and the plan for PK/PD data driven by the molecule/mechanism and study design. There are few cases when waiting for PK (+/-PD) data from the initial dose level will significantly impact subject safety or selection of the next dose but in rare circumstances where there is a rationale that this could be the case it should be implemented and documented clearly. Typically a “N-1” rolling review of PK/PD data and protocol wording supporting inclusion of PK/PD data in decision making when available should be sufficient. For key decision points within a study or between studies, e.g. to initiate multiple dose or patient cohort, the minimum PK/PD data required to support that decision should be clearly documented. 3. “Rolling review of emerging Human data during the study” – for FIH studies – this is effectively our Dose Escalation reviews - but if the scope of future guidance is expanded to other “early phase CTs” (lines 35,50,51), the EMA should consider providing additional clarification on how this would include emerging data from other studies being conducted in parallel? The practicality and logistics of this approach	A tailored approach for each case is emphasised, taking all available data into account, in a careful manner based on scientific argumentation. Integration of PK and PD data into the review, as well as safety data, are included in the guideline and an uncertainty-based approach is discussed for consideration across all aspects of a trial. The importance of cumulative data review is covered in the guideline, including comparison to preclinical data and any modeling used. PK/PD data review is also covered.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should be considered at the study/programme planning phase against its predictive value. 4. Please clarify on the parties involved in the “rolling review and the scope of the emerging human data”. This is because the scope of the emerging data is variable across FIH studies and indications.	
55	27	Comment: It is not fully clear what is meant with the “rolling review”; whether it would be the review by the sponsor / investigator of results during the study, OR whether the review by health authority of e.g. completed study parts. We are of the opinion that it is important to allow for the continuous progress of integrated protocol designs. If the first is meant, current processes are consistent with a “rolling review,” at least from Novartis' and investigator perspective; (1) Medical reviews are ongoing, with the extent and frequency of such reviews driven by the risk profile of the compound and the evolving safety data; (2) Dose escalation decisions require a systematic review of all relevant safety data at set intervals (performed by study team members including also the external investigator). In case the meaning is related to review by the Health Authority, it is essential to carefully evaluate and clarify in which instances such a review would be required. It is important to note, that the evolution in trial design to include multiple parts did not come at the cost of less stringent safety monitoring. On the contrary, safety monitoring and built-in safety mechanisms have also steadily increased over the years. Therefore, if in some particular cases the submission of results between two parts of a trial will be recommended, a notification process rather than a substantial CTA amendment should be required, allowing for a seamless continuation of the study. Start of MAD before full completion of SAD should be allowable, once a sufficient human safety margin has been reached in the SAD phase. Similarly, in oncology studies the dose expansion part of the study should be allowed to automatically proceed once the MTD/recommended Phase II dose is established, without requiring the submission of a substantial CTA or protocol amendment.	This is covered in the section on sponsor and investigator responsibilities, as well as throughout the guideline. The scenarios when a substantial amendment and regulatory review may be required are also covered.
56	10	Comments:	Considered too specific detail.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Rather than summaries of tox reports the IB should contain an integrated overview of: 1. The results of tox findings versus exposure 2. The PD versus exposure derived from in vitro/in vivo work 3. The anticipated exposure range in the FIH (instead of in IB this can be included in the protocol)	
56	10	Comments: In the last section, the IB (or protocol) should contain a list of identified risks (based on class, tox, PK properties) and proposed risk mitigation measures (biomarkers, dose schedule, population, exclusion criteria etc)	Considered too specific detail.
56	18	- General principles on key scientific information to be included in a CT application; Comment: Please explain what level of information will be required as it has the potential to markedly slow down the development of potentially promising therapies. Perhaps a discussion of the “acceptable risk benefit” based on the therapeutic area/disease under investigation e.g cancer would be a more valuable discussion.	Considered too specific detail.
57	14	Comment: Justification for safety observations for trial participants should be required and strengthened. Proposed change : Measures should be integrated into a trial protocol based on safety pharmacology core battery (S7A) and tox studies and deviations should be justified (e.g. to address why no CNS, respiratory monitoring etc. was included for the FiH study).	This is addressed in the revised guideline.

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57	18	Comment: IQ does not believe the guidance should include compulsory subject screening; this should instead be done by the sponsor as appropriate in response to the target, test article, and subject population. For example, we note that the TSSC report recommended a neuropsychological exam and cognitive tests be compulsory for screening and as a safety endpoint for monitoring and we do not believe this is justified as routine practice.	This is addressed in the revised guideline. The subject safety assessments that will be routinely conducted, their timing and any additional monitoring actions or interventions (such as radiological or PD assessments) should be pre-specified in line with the known pharmacological and non-clinical safety profile and balanced against the degree of uncertainty.
57	25	Comments: Current practices for managing emerging safety data that may impact a subject's decision to continue in a study allow for a verbal communication of the relevant information (documented) and a signed confirmation that the subject is aware of the information and willing to continue in the study in advance of updating the consent form, ethics approval and subsequent additional consent. This process is important to allow timely sharing of information when appropriate without needing to interrupt the study completely. If a clear study stopping criterion has been met, this is not relevant but for situations where it remains appropriate, this process should not be removed.	Considered too specific detail.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
57-59	35	Comment: Where similar compounds are being developed by different pharmaceutical companies, pre-clinical data, including toxicological studies, and early phase outcomes should be shared across companies.	Access to data is outside the scope of the current scientific guideline.
58	14	Comment: The handling of adverse events in relation to stopping rules and progress to next dosing steps should be specified and discussed. Proposed change: 1. Definition of adverse events of special interest should be included into a trial protocol. 2. The algorithm in case of serious adverse events (SAE) should be clearly defined, e.g. one related SAE to stop further dosing and root cause analysis to be done before re-exposure. 3. The number of AEs/SAEs in relation to stopping rules should be acceptable on a case by case basis. Such approach could be substantiated by appropriate literature (Sibille M, Br J Clin Pharmacol. 2010 Nov; 70(5): 736–748).	This is addressed in the revised guideline.
58	18	Comment: The guidance should comment on impacts of significant AEs on informed consent, and how emerging data is shared with study subjects. Proposed change: Add a bullet point on : “assessing impacts of new safety data on informed consent for currently-enrolled study participants;”	Sharing important safety data with trial subjects is included in the guideline. No change is made for AE/SAE reporting as this is determined by legislation and not a scientific guideline.

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		Comment: Regarding “Handling of AEs in relation to stopping rules and progress to next dosing steps.” Proposed change: Please clarify what is meant by this statement, and if a different process or timeline for handling of AEs is being considered.	
58	25	Comment summary: Sentinel dosing is not helpful for most NMEs, and maybe harmful if applied to compounds low on the risk continuum. Comment: 1. We believe that there is not one approach that will fit all situations with regard to the practice of sentinel dosing. The current guidance, as written, seems appropriate to apply a common sense, evidence rooted, risk-based approach to this practice. The vast majority of the time, the practice of conducting a sentinel dose will either have 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 our 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	Sentinel dosing and an uncertainty-based approach is covered in the guideline.

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		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. This is unlikely to be common. In most cases, a sentinel dose may then only result in the degradation of the research as one may not be allowed to understand the true safety of a molecule as the cohort is stopped for a false positive. Therefore, if the EMA makes any changes to this guidance, we suggest that a risk-based, totality of evidence approach be applied to a sponsor's application of sentinel dosing. The EMA should consider providing examples for consideration, such as mechanism of action, potential target, cascade activation potential, toxicology, etc. which can be clearly outlined within the guidance. Proposed guidance language: 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. Accordingly, 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).	
59	14	Comment: The general principles on communication to competent authorities and CT subjects should be clarified and	General principles on communication are

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		discussed. Proposed change: It should be made clear for an applicant when agency/ethics committee should be involved e.g. via an amendment, and the underlying concept should be discussed (notification only, review, approval).	covered in the guideline where appropriate but reporting requirements to the regulatory authorities are covered by legislation and not a scientific guideline. The scenarios when a substantial amendment and regulatory review may be required are covered. Factors within the usual remit of an Ethics Committee are not covered as this is a scientific guideline.
59	25	Comment: suggest rewording (minor) Proposed change: <i>“General Principles on appropriate and timely communication to competent authorities and CT subjects.”</i>	Text in concept paper not subject to change (see above).
59	25	Comments: 1. The FIH Guidance mentions that SUSAR communication is important and that sponsors should ensure that processes are in place (section 4.4.2.8). Reference is given within this section to Directive 2001/20/EC.	General principles on communication are covered in the guideline

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		Expedited reporting is covered in ICH E2A “Clinical Safety Data Management (CHMP/ICH/377/95): Definitions and Standards for Expedited Reporting”. This ICH Guidance (E2A) provides expedited reporting timeframes in section III.B consistent with Directive 2001/20/EC. We believe the 7-day and 15-day timeframes are sufficiently discussed and are clear. The phrase “as soon as possible” is used within both reporting sections. However, the latest timeframe given of 7 and 15 days is generally viewed as the reporting requirement. If considered as new finding likely to affect the safety of the subjects, fatal/life threatening or leading to hospitalisation SUSAR (see comment below), the sponsor and investigator shall take appropriate Urgent Safety Measures to protect the subjects against an immediate hazard. In that case sponsor shall forthwith inform CA and ensure EC are notified of those new events and of the measures (Art. 10 (b) Directive 2001/20/EC). 2. If the Agency expects sponsors to report fatal or life-threatening SUSARs sooner than 7 days with FIH trials, this point could be emphasised within the FIH Guidance with reference to ICH E2A or Directive 2001/20/EC. The full discussion on expedited reports should remain within ICH E2A and not duplicated within the FIH Guidance, however. Consequently, International Pharmacovigilance declaration rules should be established in order to qualify as a new finding any event causing the death or hospitalisation of a healthy volunteer presumed to be related to trial. Such event should lead to the immediate evaluation of potential causality by both the sponsor and the investigator. If there is sufficient certainty of the lack of relatedness, the trial may proceed. Otherwise, suspension of the administration of the treatments to all participants until their safety can be guaranteed. In the latter case, it may be necessary to revise and repeat informed and written consent prior to any resumption of the study. Immediate declaration of such event to Competent Authorities / Ethics Committees should be requested (+ additional pertinent information within 8 days). “general principles on communication to competent authorities and CT subjects “ and Line 58 “handling of adverse events in relation to stopping rules and progress to next dosing steps” – Both highlight an identified need for robust communication between all relevant organisations – Site <-> sponsor and site and or	where appropriate but reporting requirements to the regulatory authorities are covered by legislation and not a scientific guideline.

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		Sponsor to CA and subjects. Even if all possible scenarios cannot be accounted for, advice on expectations for site <-> Sponsor (medical Monitor/medical oversight) might be useful.	
60-65	26	Comment: It will be necessary to highlight how this guideline will be articulated and thus used with other existing guidelines. In particular, the European Commission adopted detailed guidelines on good clinical practice specific to advanced therapy medicinal products. Although the latter would need to be updated, the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products' should either refer to guidelines on good clinical practice specific to advanced therapy medicinal products or explicitly consider the risks for first-in-human clinical trials with investigational advanced therapy medicinal products.	This is addressed in the revised guideline with appropriate referencing.
63	26	Comment: We understand and welcome the understanding that a risk-based approach should be an umbrella principle for the revised guideline, especially for the phasing of first-in human clinical trials. However, the 'risk-based approach' refers to a specific optional strategy that has been established for advanced therapy medicinal products. In that context, specific guideline has been adopted: Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products (EMA/CAT/CPWP/686637/2011) Therefore, the EMA should be very cautious when using this particular expression of 'risk-based approach' so there is no confusion for stakeholders regarding the numerous guidelines that apply to medicinal products. Moreover, it will be useful to highlight how this integration is actually expected to be done. Proposed change: "in an integrated approach taking into account the risks involved."	Reference in the guideline is to an uncertainty-based approach related to the IMP. ATMPs are outside the scope of this guideline.

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64-65	6	Proposed change: there is a need to emphasise emphasize that the guideline is applicable for all molecules and not only for biotechnology-derived proteins.	This is addressed in the scope of the document.
66	25	Comment: 1. We support EMA's focus within this concept paper on the important general aspects of first-in-human studies. Nevertheless, EFPIA believes it necessary to provide appropriate guidance on the evolving arena of phase 1 studies involving neonatal/paediatric/adolescent patients. However, given the exceptional circumstances specific to this population, EFPIA contends that paediatric phase 1 study considerations should be addressed in a separate guidance rather than the general first-in-human guidance resulting from this consultation. A separate approach would better facilitate direct engagement of the paediatric research and development community. 2. Concern that guidance does not have sufficient recommendations on timing of pre-clinical juvenile studies and FIH studies in children relative to development of adult indications. If EMA agrees with separate guidance for phase 1 pediatric/adolescent guidance the concept paper might include a statement that indicates the following concepts and then to reference the development of the separate guidance: Proposed change: 1. If the product is being developed for an indication that occurs in both children and adults, the goal should be concurrent licensure unless there are safety concerns that would delay or even preclude paediatric studies.	The issue is addressed in the revised guideline. Reference is made to trials in the paediatric population. The guideline is meant to inform how FIH can be as safe as possible; it is beyond the scope to suggest or prescribe the goal of the development.
66	25	Comment: • For some products (serious diseases in adults and children for which sufficient treatment does not exist), the development program needs to be conducted early in pediatric population (after safety and tolerability	The issue is addressed in the revised guideline. Reference is made to trials in the paediatric

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		data have been obtained in adults) - For other products, pediatric studies can be initiated once efficacy and safety have been studied and proved in adults. - If the product is being developed for a paediatric indication alone (if no comparable adult indication exists) preclinical data must be developed to support sufficient prospect of direct benefit to justify the risks of the experimental intervention (which varies with the severity of the disease and the adequacy of alternate treatments) before initiation of paediatric clinical trials. - Given the exceptional circumstances specific to paediatric population paediatric phase 1 study considerations will be provided in a separate guidance.	population. The guideline is meant to inform how FIH can be as safe as possible; it is beyond the scope to suggest or prescribe the goal of the development.
72	10	Comments: Specific risk factors: Since most cases of death in healthy volunteers were due to non-IMPs, ACRO suggests mentioning that risk identification should also be done for non-IMPs and any hazardous study procedures. Specific risk factors: irreversible binding, delayed PD, exposure in case the FiH formulation has a much higher F, there is a considerable FE (30 fold observed recently) or the free fraction in humans is much higher. Specific risk factors: Preclinical data on specificity is not mentioned in the guideline (nor in any other guideline). ACRO thanks the Agency for the opportunity to comment on this Concept Paper and looks forward to the Agency's public consultation on the revised draft guideline later this year. Please contact ACRO if we can provide any additional information (knoonan@acrohealth.org).	A statement is included in the revised guideline that risks during FIH/early CTs not only come from the IMP but also from e.g. challenge agents, or invasive study procedures. These should be considered in any assessment of risk.
other	25	Comments: Include language in the revised guidance that addresses the extent of off-target and closely-related off-target	Off-target binding is addressed in the revised

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		screening that is required. For example, running a standard CEREP panel for a covalent enzyme inhibitor will give you selectivity over ~65 mostly unrelated targets, but will not detect liabilities for binding to other targets closely related to the primary pharmacology (e.g. other serine hydrolases). Proposed changes: Off target screening should include selectivity and potency measures of a wide array of unrelated receptors and targets that could produce human AE's, but should also include an examination of off-target pharmacology that is closely related to the primary pharmacology (e.g. protein isoforms or enzyme and receptor subtypes). Functional assays should also be considered where relevant. CTAs should include a detailed description of the off-target pharmacology assessed and the potency relative to the primary pharmacology. A discussion may also be included regarding how the off-target pharmacology impacts the safety profile and relevance to clinical risk given the choice of clinical trial subjects/patients (if latter included in FIH).	guideline.
other	25	Comments: The concept paper does not speak to special safety considerations for irreversible binders as drugs. See proposed language for specific recommendations. Proposed changes: When irreversible binders or compounds with extremely long PD effect (long PD half-lives or slow off-rate) are advanced to clinical testing, special considerations should be addressed for this class of drugs and include: species differences in target turnover as it relates to dose frequency in SAD/MAD trials, washout period and whether separate cohorts through SAD/MAD are needed with no subject crossover. The time dependence of covalent or irreversible inhibitors when extrapolating efficacy and toxicology, target turnover rates should be incorporated into PK/PD models and recognize that the rate of target turnover may influence the onset/duration of AE's and may occur at lower or higher concentrations and timeframes than in the toxicology	Irreversible binding and degree of uncertainty is addressed in the revised guideline.

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		species. Further, covalent inhibitors should be screened in general reactivity assays and appropriate target panels to determine the selectivity and reactivity profile.	
other	25	Comments: We do not believe there need to be any changes to metabolite safety testing and monitoring in the scope of revisions.	Comment noted.

