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4 **Guideline on strategies to identify and mitigate risks for**
5 **first-in-human and early clinical trials with investigational**
6 **medicinal products**

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8 Draft

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65 **Executive summary**

66 This is the first revision of the ‘Guideline on strategies to identify and mitigate risks for first-in-human
67 clinical trials with investigational medicinal products’.

68 The revision is intended to further assist sponsors in the transition from non-clinical to early clinical
69 development and identifies factors influencing risk for new investigational medicinal products (IMPs).
70 The document includes considerations on quality aspects, non-clinical and clinical testing strategies
71 and designs for first-in-human (FIH) clinical trials (CTs) and early phase CTs (see section 2). Strategies
72 for mitigating and managing risks are given, including principles on the calculation of the starting dose
73 to be used in humans, the subsequent dose escalation, the criteria for maximum dose and the conduct
74 of the CT including the conduct of multiple parts.

75 **1. Introduction (background)**

76 Traditionally FIH CTs were most associated with a single ascending dose (SAD) design, which were
77 subsequently followed by a multiple ascending dose (MAD) CT. Since then, integration of the non-
78 clinical data available before FIH administration and the pharmacokinetic (PK), pharmacodynamic
79 (PD) and human safety data emerging during a trial has evolved. Consequently, the increasing
80 practice is to perform FIH trials and early phase CTs with integrated protocols that combine a number
81 of different study parts (e.g. SAD, MAD and food effects).

82 In FIH/early CTs subjects are not expected to derive therapeutic benefit, except in certain patient
83 populations. The aim should always be the safety and well-being of the trial subjects, whether patients
84 or healthy individuals.

85 Quality aspects of the IMP should not, in themselves, be a source of risk for CTs. Nevertheless,
86 special consideration should be given to certain factors which may add to the risk as described in this
87 guideline.

88 The non-clinical testing and experimental approaches for FIH/early CTs are used to identify factors
89 influencing the risks associated with an IMP.

90 Special attention should be given to the estimation of the initial dose to be used in humans and to the
91 subsequent dose escalations to a predefined maximum dose. It should be noted that the expected
92 exposure in humans at a dose to be given, in comparison to the exposure at which certain effects
93 were observed in animals or earlier in the study in humans, is considered important. Therefore,
94 whenever dose is mentioned in this guideline, the expected exposure at that dose should always be
95 taken into consideration.

96 In defining an appropriate development programme for an IMP, information on safety needs to be
97 integrated from many sources and reviewed in an iterative process. Strategies for development of a
98 new medicine and the experimental approaches used to assemble information relevant to the safety
99 of CTs should always be science-based, and decisions should be made and justified on a case-by-case
100 basis. In those cases where an integrated protocol is used in a FIH CT, it is important to remember
101 that data generated during the trial should also be used to inform the decision processes for the
102 continuation of dosing.

103 2. Scope

104 This guideline covers non-clinical and quality issues for consideration prior to the first administration in
105 humans and the design and conduct of CTs that generate first knowledge in humans during the early
106 clinical development. The early phase CTs include, in this guideline, those which generate initial
107 knowledge in humans on tolerability, safety, PK and PD after SAD or MAD. These trials may also
108 include collection of data on food interaction, in different age groups as well as early proof of concept
109 (PoC) or early proof of principle (PoP) parts and bioequivalence of different formulations. These trials
110 are often undertaken in healthy volunteers but can, in certain situations, also include patients.

111 The current revision concerns the extension of the existing EU guidance to address FIH and early
112 phase CTs with integrated protocols, and recommendations regarding the non-clinical and emerging
113 clinical PK, PD and safety data to support them.

114 The guideline applies to all new chemical and biological IMPs. While many of the scientific principles
115 included in this guideline apply to advanced therapy investigational medicinal products as well, these
116 products are not included in the scope of this guideline.

117 3. Legal basis

118 This guideline applies to relevant Clinical Trial Applications (CTAs) submitted in accordance with
119 Directive 2001/20/EC, which will be repealed by Regulation (EU) No 536/2014. The guideline should be
120 read in conjunction with Directive 2001/83/EC and all other pertinent elements outlined in current and
121 future EU and ICH guidelines and regulations, in particular:

- 122 • EudraLex - Volume 10 - Clinical trials guidelines.
- 123 • EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines. In particular, Annex 13:
124 Manufacture of Investigational Medicinal Products.
- 125 • Guideline on virus safety evaluation of biotechnological investigational medicinal products
126 (EMA/CHMP/BWP/398498/2005-corr.).
- 127 • Guideline on the requirements to the chemical and pharmaceutical quality documentation
128 concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004).
- 129 • Guideline on the requirements for quality documentation concerning biological investigational
130 medicinal products in clinical trials (CHMP//BWP/534898/2008).
- 131 • Clinical investigation of medicinal products in the paediatric population (ICH E11).
- 132 • Evaluation of anticancer medicinal products in man (CPMP/EWP/205/95 Rev.4).
- 133 • Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing
134 authorization for pharmaceuticals (ICH M3(R2)) and related Q&A document.
- 135 • Note for guidance on toxicokinetics: the assessment of systemic exposure in toxicity studies -
136 questions and answers (ICH S3A).
- 137 • Pharmacokinetics: Guidance for repeated dose tissue distribution studies (ICH S3B).
- 138 • Preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6(R1)).
- 139 • Non-clinical evaluation for anticancer pharmaceuticals (ICH S9) and related Q&A document.

- 140 • Guideline for good clinical practice (ICH E6(R2)). November 2016.
- 141 • Questions and Answers by the CTFG on clinical trials. Head of Medicines Agencies' Clinical trial
142 facilitation group. January 2012.
- 143 • Safety pharmacology studies for human pharmaceuticals (ICH S7A).
- 144 • Non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval
145 prolongation) by human pharmaceuticals (ICH S7B).
- 146 • Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on
147 the protection of animals used for scientific purposes.

148 **4. General considerations**

149 When planning FIH/early CTs, sponsors and investigators should identify the potential factors of risk
150 and apply appropriate risk mitigation strategies. These factors should be addressed appropriately for
151 all FIH/early CTs in the sponsor's CTA.

152 Factors of risk may be derived from particular knowledge or lack thereof regarding the mode of
153 action, the nature of the target, the relevance of animal models and/or findings in non-clinical safety
154 studies.

155 **4.1. Mode of action**

156 While a novel mode of action might not necessarily add to the risk per se, consideration should be
157 given to the novelty and extent of knowledge of the supposed mode of action, as well as the
158 characteristics of the target. This includes the nature and intensity of the effect (e.g. extent,
159 amplification, duration, (ir)reversibility) and other mechanistic effects of the IMP on the intended
160 target(s) and potential off-targets. The type and steepness of the dose response relationship as
161 measured in experimental systems, which may be linear within the dose range of interest, or non-
162 linear (e.g. plateau with a maximum effect, over-proportional increase, U-shaped, bell-shaped, time
163 dependent), are of particular importance.

164 For example, the following aspects might require special attention:

- 165 • A mode of action that involves a target that is associated to multiple signalling pathways (target
166 with pleiotropic effects), e.g. leading to various physiological effects, or targets that are
167 ubiquitously expressed, as often seen in the immune or nervous system.
- 168 • A biological cascade or cytokine release including those leading to an amplification of an effect
169 that might not be sufficiently controlled by a physiologic feedback mechanism (e.g. in the
170 immune system or blood coagulation system).
- 171 • A mode of action that involves irreversible or long lasting binding to the primary target, either
172 due to pharmacological action or the PK profile of the compound. For instance, if the duration of
173 the pharmacological activity is linked to regeneration of the receptor, rather than being related to
174 the PK profile of the molecule.

175 When analysing risk factors associated with the mode of action, aspects to be considered may
176 include:

- 177 • Previous exposure of humans to compounds that have similar or related modes of action.

- 178 • The usefulness of PD data following repeated dosing testing. While single dose PD data can be
179 used for an initial interpretation of the potential outcome of multiple dosing, consideration should
180 be given to conducting repeated dose pharmacology studies or to include PD endpoints in
181 repeated dose toxicity studies.
- 182 • Evidence from animal models (e.g. knock-out, transgenic or humanised animals) for the potential
183 risk of serious pharmacologically-mediated toxicity.
- 184 • Novelty of the molecular structure of the active substance(s), for example a new type of
185 engineered structural format, such as those with enhanced receptor interaction as compared to
186 previously characterised compound(s).

187 **4.2. Nature of the target**

188 Beyond the mode of action, the nature of the target itself might impact on the potential risk inherent
189 to the initial administrations to humans. Sponsors should carefully review and discuss any potential
190 risks associated with the intended target in humans, which should include the following aspects,
191 based on the available data:

- 192 • The extent of the available knowledge on the structure, tissue distribution (including expression
193 in/on cells of the human immune system), cell specificity, disease specificity, regulation, level of
194 expression, and biological function of the human target including “down- stream” effects, and
195 how it might vary between individuals in different populations of healthy subjects and patients. If
196 such data are limited, this should be highlighted.
- 197 • If possible, a description of polymorphisms of the target in relevant animal species and humans,
198 and the impact of any such polymorphisms on the pharmacological effects of the medicinal
199 product.
- 200 • Potential off-target effects, with particular focus on, but not limited to, targets closely
201 related/similar to the intended one.

202 **4.3. Relevance of animal species and models**

203 The sponsor should discuss the relevance of the non-clinical models to humans taking into account the
204 target, its structural homology, distribution, signal transduction pathways and the nature of
205 pharmacological effects (See section 6.1).

206 **4.4. Findings in non-clinical safety studies**

207 The findings in non-clinical safety studies that are considered to be relevant to humans should
208 carefully be considered when designing FIH/early CTs (See section 6.5).

209 **5. Quality aspects**

210 The requirements regarding physico-chemical characterisation are the same for all IMPs with additional
211 biological characterisation of biological products.

212 Specific areas to be addressed include determination of strength and potency, qualification of the
213 material used and reliability of very small doses.

214 **5.1. Determination of strength and potency**

215 To determine a safe starting dose, the methods used for determination of the strength and/or the
216 potency of the product need to be relevant, reliable and qualified. As major clinical decisions are based
217 on the non-clinical data, it is important to have a representative defined reference material early in the
218 development programme to appropriately measure biological activity.

219 **5.2. Qualification of the material used**

220 The material used in non-clinical studies should be representative of the material to be used for
221 FIH/early CT administration. It is important to have an adequate level of quality characterisation even
222 at this early point of development. A characterisation of the product including its heterogeneity,
223 degradation profile and process-related impurities should be performed. Special consideration should
224 be given to the suitability and qualification of methods to sufficiently characterise the active substance
225 and drug product.

226 **5.3. Reliability of very small doses**

227 Applicants should demonstrate that the intended formulation of the doses is suitable. There is a risk of
228 reduced accuracy in cases where the medicinal product needs to be diluted, to prepare very small
229 doses, or the product is provided at very low concentrations as the product could be adsorbed to the
230 wall of the container or infusion system. The compatibility of the product with primary packaging
231 materials and administration systems should be discussed.

232 **6. Non-clinical aspects**

233 The quality of documents supporting the CT application should be state-of-the-art in format (e.g. as
234 per Good Clinical Practice (GCP)) and scientific content thus providing adequate information on the
235 performed non-clinical studies to allow for a meaningful assessment. The inclusion of a tabulated
236 summary containing an overview of all relevant non-clinical data is encouraged.

237 The sponsor should confirm that all pivotal non-clinical safety studies in support of the CT application
238 are conducted in compliance with Good Laboratory Practice (GLP). All other studies (e.g. PK and PD)
239 should be of high quality and consistent with the principles of GLP.

240 In accordance with the 3Rs principles on animal use (Directive 2010/63/EU), a scientifically
241 satisfactory method or testing strategy, not entailing the use of live animals should be used wherever
242 possible. The use of in vitro studies, including studies using human material, is encouraged whenever
243 possible.

244 **6.1. Demonstration of relevance of the animal model**

245 The search for a relevant animal model should be documented and the model selected should be
246 justified in the Investigator's Brochure (IB).

247 The demonstration of relevance of the animal model(s) may include comparison with humans of:

- 248 • target expression, distribution and primary structure. However, a high degree of homology does
249 not necessarily imply comparable effects;
- 250 • pharmacodynamics;

- 251 • metabolism and other PK aspects;
- 252 • tissue cross-reactivity studies using human and animal tissues (e.g. monoclonal antibodies).

253 Animal models of disease that are thought to be similar to the human disease may provide further
254 insight into pharmacological action and PK (e.g. disease-related expression of the target) as well as
255 dosing in patients and safety (e.g. evaluation of undesirable promotion of disease progression).
256 Therefore, in certain cases, studies performed in animal models of disease may be used as an
257 acceptable alternative to toxicity studies in normal animals. The scientific justification for the use of
258 these animal models of disease to support safety should be provided.

259 Non-clinical studies in non-relevant species may give rise to misinterpretation and are discouraged.
260 Where no relevant species exists, the use of homologous proteins or the use of relevant transgenic or
261 humanised animals expressing the human target should be considered. The data gained from these
262 models might be more informative when the interaction of the IMP with the target has similar
263 physiological consequences to those expected in humans. The use of in vitro human cell systems could
264 provide relevant additional information, especially for the translation of the mode of action from animal
265 to human.

266 Qualitative and quantitative differences may exist in biological responses to a new IMP in animals
267 compared to humans. For example, there might be differences in affinity of the new candidate for
268 molecular targets, but also physiological differences in tissue distribution of the molecular target,
269 cellular consequences of target binding, cellular regulatory mechanisms, metabolic pathways, or
270 compensatory responses to an initial physiological perturbation.

271 Where there is evidence of species-specificity of action from in vitro studies with human cells
272 compared with cells from a test species, the value of the in vivo response of the test species may be
273 significantly reduced in terms of predicting the in vivo human response. It should be noted that a
274 similar response in human and animal cells in vitro is not necessarily a guarantee that the in vivo
275 response will be similar.

276 In practice this means that non-clinical studies with highly human-specific medicinal products may:

- 277 • not reproduce the intended human pharmacological effect in animals;
- 278 • give rise to misinterpretation of PK and PD results;
- 279 • not identify relevant toxic effects.

280 A weight-of-evidence approach should involve integration of information from in vivo, ex vivo and in
281 vitro studies into the decision-making process.

282 High human-specificity of a medicinal product makes the non-clinical evaluation of the risk to humans
283 more difficult, but does not imply that there is always an increased risk in FIH/early CTs. However, in
284 these cases, a proper discussion of the potential risks should be given to justify the conduct of a CT.

285 **6.2. Pharmacodynamics**

286 Primary PD studies should address the mode of action related to therapeutic use and provide
287 knowledge on the interaction of the IMP with the intended target as well as with related targets.

288 The selectivity and specificity of the IMP as well as secondary pharmacodynamics, defined as effects of
289 the IMP on other than the desired therapeutic targets, should be critically evaluated and documented.
290 This might also include effects on other downstream or physiologically integrated endpoints.

291 The primary and secondary PD should be conducted in vitro, using animal and human-derived material
292 and in vivo using animal models, as relevant. These studies should include target interactions
293 preferably linked to functional response, e.g. receptor binding and occupancy, inhibition of enzymes,
294 duration and (ir)reversibility of effect, dose-response relationships and physiological turn-over of the
295 target.

296 Data on the functionality of additional functional domains in animals, e.g. Fc receptor system for
297 monoclonal antibodies, should be present.

298 A dose/concentration-response curve of the pharmacological effect(s) should be established with
299 sufficient titration steps to detect significant pharmacological effects.

300 A state-of-the-art PK/PD modelling approach is recommended, taking into consideration repeated dose
301 applications as to be expected in the clinical situation.

302 **6.3. Pharmacokinetics**

303 PK and toxicokinetic (TK) data, as per ICH S3, S6(R1), S9, M3(R2) and respective Q&A documents (if
304 present), should be available in all species used for the non-clinical safety studies conducted and
305 should adequately support the interpretation of data from in vivo PD models before starting FIH/early
306 CTs. Sponsors should supply a brief summary of the analytical assays used to characterise the non-
307 clinical PK and TK, including their accuracy, precision and limits of quantification.

308 Systemic exposures at pharmacodynamically active doses in the relevant animal models should be
309 determined and considered especially when PD effects are suspected to contribute to potential safety
310 concerns.

311 **6.4. Safety pharmacology**

312 Standard core battery data should be available before the first administration in humans as outlined in
313 ICH guidelines S7A, S7B, S6(R1), S9, M3(R2) and related Q&As.

314 Additional studies to investigate effects in these and other organ systems should be conducted on a
315 case-by-case basis where there is a cause for concern, e.g. in case of low selectivity of the IMP for its
316 primary target.

317 **6.5. Toxicology**

318 The toxicology programme should be performed in relevant animal species (see section 6.1) and
319 include TK as discussed in section 6.3.

320 When factors influencing risk are identified (see sections 4 and 6.2.), the inclusion of additional
321 endpoints to the toxicology studies should be considered.

322 Toxicity can be the result of exaggerated pharmacological actions. However, these types of effects
323 should not be ignored when establishing a safe starting dose for humans and the corresponding
324 exposure will contribute to the determination of the dose escalation range to be investigated in
325 humans. Primary and secondary PD can support the generation of mechanistic hypotheses regarding
326 the toxicities seen in vivo and help in the interpretation of the human relevance of these findings.

327 An evaluation as to whether the target organs identified in the non-clinical studies warrant particular
328 monitoring in the CT should be undertaken. Serious toxicity should lead to a more cautious approach

329 when setting doses in the FIH/early CTs. If mortalities and/or serious toxicity are observed in non-
330 clinical studies, an evaluation of putative mechanism of toxicity and/or cause of death is expected to
331 be addressed (e.g. consideration of histopathological examination of deceased animals, which is
332 certainly necessary in pivotal studies and should also be considered for dose range finding studies).

333 **7. Dosing selection for FIH and early clinical trials**

334 **7.1. General aspects**

335 Careful dosing selection of an IMP is a vital element to safeguard the subjects participating in FIH and
336 early CTs. Dose selection should also take into account a reasonably rapid attainment of the trial
337 objectives (e.g. assessment of tolerability, PD or PK profile) without exposing large numbers of
338 subjects.

339 All available non-clinical information (PD, PK, TK and toxicological profiles, dose or exposure/effect
340 relationships, etc.) should be taken into consideration for the calculation of the starting dose, dose
341 escalation steps and maximum dose. Furthermore, clinical data (e.g. PK, PD and reports of adverse
342 events) emerging during the trial from previous dosed cohorts/individuals needs to be taken into
343 account, in line with pre-specified decision criteria. Experience, both non-clinical and clinical, with
344 molecules having a similar mode of action can also be useful.

345 The starting dose and estimated exposure levels chosen for all cohorts and study parts should be pre-
346 specified and a justification for these steps should be outlined in the study protocol. Submission of a
347 substantial amendment(s) can be used, if required, to adjust the predefined dosing selection,
348 depending on data emerging during the CT. Substantial amendments will also be needed where dose
349 escalation has reached a pre-defined maximum exposure and the absence of clinical effects leads to a
350 conclusion that further careful escalation is warranted.

351 The methods used and calculations on how doses and estimated exposure levels were determined,
352 including methods for modelling (e.g. PK/PD and physiologically-based pharmacokinetic (PBPK)) should
353 be included in the IB and summarised in the protocol.

354 For starting and maximum doses for Exploratory Clinical Trials, reference is made to ICH M3(R2). If an
355 IMP has been administered to humans under the paradigm of microdose trials, as outlined in ICH
356 M3(R2), any subsequent study using a non-microdose should be considered within the scope of this
357 guideline.

358 **7.2. Starting dose**

359 In general, the no observed adverse effect level (NOAEL) should be determined in the non-clinical
360 safety studies performed. The exposures achieved at the NOAEL in the most relevant and sensitive
361 animal species used should then be used for estimation of an equivalent exposure for humans.
362 Estimation should be based on state-of-the-art modelling (e.g. PK/PD and PBPK) and/or using
363 allometric factors.

364 Exposure showing PD effects in the non-clinical pharmacology studies, including ex vivo and in vitro
365 studies in human tissues if feasible, should also be determined and these data should be used to
366 determine the minimal anticipated biological effect level (MABEL) in humans and an estimation of the
367 pharmacologically active dose (PAD) and/or anticipated therapeutic dose range (ATD) in humans.
368 When using these approaches, potential differences in sensitivity for the mode of action of the IMP
369 between humans and animals need to be taken into consideration. In addition, the calculation of the

370 MABEL, PAD and/or ATD should consider target binding and receptor occupancy studies in vitro in
371 target cells from human and the relevant animal species and exposures at pharmacological doses in
372 the relevant animal species. Whenever possible, all relevant data should be integrated in a suitable
373 modelling approach for the determination of the MABEL, PAD and/or ATD.

374 In order to further limit the potential for adverse reactions in humans, a safety factor(s) is generally
375 applied in the calculation of the starting dose in humans.

376 Safety factors should take into account potential risks related to the novelty of the active substance,
377 its pharmacodynamic characteristics, including irreversible or long lasting findings and the shape of the
378 dose-response curve, the relevance of the animal models used for safety testing, uncertainties related
379 to the estimation of the MABEL, and the expected exposure in humans. Furthermore, findings in the
380 non-clinical studies and how well potential target organ effects can be monitored in the CT should also
381 be addressed and may influence the safety factors used.

382 Any safety factors used should be justified and detailed in the IB and protocol.

383 When the methods of calculation (e.g. NOAEL and MABEL) give different estimations of the starting
384 dose for humans, the lowest value should be used, unless justified. Such a justification should be
385 included in the IB and CT protocol.

386 In healthy volunteers, the starting dose should ideally result in an exposure to a subject that is below
387 that which would be expected to produce a PD response.

388 **7.3. Dose escalation**

389 Dose increases at any time during a CT should always be justified and outlined in the protocol (see
390 section 8.2.9). The choice of the subsequent dose levels should include some estimate of the potential
391 PD effects and exposure levels to be achieved as well as adverse effects seen (if any). The calculated
392 PAD/ATD should also be taken into account. The dose increment between two dose levels should be
393 guided by the dose/exposure-toxicity or the dose/exposure-effect relationship defined in non-clinical
394 studies and by emerging clinical data. The steeper the increase in the dose/toxicity or dose/effect
395 curves, or if there are uncertainties in the estimations of these relationships, the lower the dose
396 increment should be selected. Another factor for consideration is the reliability with which potential
397 adverse effects can be monitored in humans before they escalate into something serious/irreversible.
398 Furthermore, if there is evidence of non-linear PK, smaller dose increments, particularly in the later
399 parts of SAD/MAD, should be considered. If emerging clinical data reveal significant differences from
400 non-clinical or modelling and simulation data, a substantial amendment may be required to adjust
401 planned dose levels unless this possibility was discussed including predefined decision criteria and
402 approved in the protocol.

403 Any dose skipping should take aspects such as steepness of dose-response curve or saturation of
404 target into account and requires a substantial amendment.

405 **7.4. Maximum dose and dose range**

406 The design of FIH or early CTs often aims to determine a dose or exposure-response curve for the
407 most relevant pharmacological effect(s), and includes a maximum predefined dose or exposure
408 margin. Deviations from this principle should be justified and may lead to more cautious approaches.

409 A maximum dose or exposure, which should not be exceeded in the study without approval of a
410 substantial amendment, should be pre-defined and justified in the protocol for the full CT and/or each

411 study part. This justification should be based on all available non-clinical and clinical data, including
412 PD, PK, findings in toxicity studies and exposure at the expected therapeutic dose range. In addition, if
413 non-clinical data or modelling data indicate a plateauing of exposure, this should be taken into account
414 for the defined maximum dose, regardless as to whether increasing of doses is viewed as a safety
415 concern.

416 For integrated protocols, where it may not be possible to predefine definite doses in all study parts, a
417 clear statement should be included that the doses will be chosen based on predefined (dose selection)
418 criteria. These criteria should integrate data from previous study parts once these are completed and
419 should not exceed the maximum exposure unless justified by the sponsor when requesting a
420 substantial amendment (see also stopping criteria in section 8.2.10).

421 If an absolute maximum dose cannot be provided, then this should be justified and the maximum fold-
422 increase in dose from one cohort to the next should be clearly stated as well as a maximum number of
423 cohorts to be evaluated. A maximum exposure limit would be expected in this situation.

424 In general, the exposure at the expected human therapeutic dose range should not be exceeded in
425 studies in healthy volunteers, unless scientifically justified.

426 Target saturation should be taken into account, e.g. if the intended therapeutic effect is linked to
427 enzyme inhibition, then the maximum dose should consider when complete inhibition is achieved and
428 no further therapeutic effect is to be expected by increasing the dose.

429 For trials or trial parts that include patients, the maximum tolerated dose (MTD) (if applicable) should
430 be clearly defined and not be exceeded once it has been determined. The potential
431 therapeutic/clinically relevant dose (exposure) and the expected benefit/risk balance should always be
432 considered when defining the dose range. A trial design using a MTD approach is considered to be
433 unethical for healthy volunteers.

434 **7.5. Moving from single to multiple dosing**

435 The selection of an appropriate dosing interval and duration of dosing for all multiple dosing cohorts
436 and study parts should take into account the specific PK and PD characteristics of the IMP, the
437 available non-clinical safety data, and human PK, PD and safety data from subjects in previous single
438 dose cohorts. Particular attention should be paid to linear versus non-linear PK in the expected
439 concentration range, the PK half-life versus duration of action and the potential for accumulation.

440 Cohorts administered multiple doses can explore different dosing regimens and allow for flexibility in
441 the dosing schedule, such as a move from once daily dosing to twice daily dosing. However, previous
442 MTD doses (and corresponding exposure and/or effects) should not be exceeded and a maximum
443 duration of dosing should be stated in the protocol for every cohort. The chosen dose, as well as
444 expected exposure after multiple dosing (C_{max} and AUC_{0-t}), should have been covered during preceding
445 SAD parts/trials. If, however, emerging clinical data following multiple dosing suggests tolerance to
446 adverse effects seen in a SAD part of a study, a substantial amendment to the protocol to cover higher
447 doses in a MAD part can be considered.

448 **7.6. Route of administration**

449 The choice of route of administration for dosing in humans should be justified based on the non-clinical
450 data.

451 In the case of an intravenous administration, a slow infusion may be more appropriate than a slow
452 bolus. This would allow for a timely discontinuation of the infusion to mitigate an adverse outcome.

453 **7.7. Patients**

454 Similar considerations for the starting dose as outlined in section 7.2 apply. The goal of selecting the
455 starting dose for FIH/early CTs in patients, i.e. where there are no previous data in healthy volunteers,
456 is to identify a dose that is expected to have a minimal pharmacological effect and is reasonably safe
457 to use. The starting dose should also take into account the nature of disease under investigation and
458 the severity of the disease in the patient population included in the CT. In some instances, a starting
459 dose that is substantially lower than the human expected therapeutic dose may not be appropriate. If
460 a higher dose is proposed, a rationale should be provided and the subjects included in the CT should
461 be informed.

462 When moving from healthy volunteers to patients, consideration should be given to reverting to a
463 single dose design (with dose escalation as appropriate) in the first patient cohort.

464 Other approaches may also be considered in specific situations, e.g. for studies with conventional
465 cytotoxic IMPs in oncology patients (see ICH S9). In general, the highest dose or exposure tested in
466 the non-clinical studies may not limit the dose-escalation or highest dose investigated in a CT in
467 patients with advanced cancer and also in other life limiting diseases if appropriately justified.

468 Furthermore, some special populations, such as the paediatric population, may deserve additional
469 specific considerations (as per ICH E11).

470 **8. Planning and conduct of FIH and early clinical trials**

471 **8.1. General aspects**

472 The overall study design should be scientifically justified and careful consideration should be given to
473 the inclusion of each study part considering the data each will provide and the time available for
474 integrated assessment. Safety should not be compromised in the interests of speed of acquiring data
475 or for logistical reasons.

476 Risk mitigation activities should be proportionate to the potential risks identified. Key aspects of the
477 trials should be designed to mitigate identified risk factors, including but not limited to:

- 478 • study population (see section 8.2.3);
- 479 • first/starting dose, maximum dose and maximal duration of the treatment;
- 480 • route and rate/frequency of administration;
- 481 • the half-life (PK/PD) of the IMP if the same subjects are participating in multiple cohorts;
- 482 • number of subjects per dose increment (cohort);
- 483 • sequence and interval between dosing of subjects within the same cohort;
- 484 • dose escalation increments;
- 485 • transition to next dose cohort or next study (part);
- 486 • stopping rules;

487 • trial sites (see section 8.4).

488 It is recognised that placebo is often included as part of the design of FIH/early CTs.

489 It is recommended that a PD measure is included, when appropriate and feasible, in order to facilitate
490 the link with the non-clinical experience and support dose escalation decisions.

491 **8.2. Protocol**

492 **8.2.1. Overall design**

493 The protocol should describe the strategy for managing risk including a specific plan to monitor for and
494 manage likely AEs or adverse reactions as well as the procedures and responsibilities for modifying or
495 stopping the trial if necessary. If there is an integrated protocol there should be a decision at a
496 predefined time point on proceeding to the next part.

497 Graphical representation of the overall scheme of the proposed trial in real-time showing intervals to
498 allow rolling review, timing of all reviews and decision points, as well as any overlap between phases
499 or parts is encouraged.

500 Details on the size of the cohorts, including how many subjects are on active and how many are on
501 placebo treatment should be included and justified.

502 **8.2.2. Integrated protocols**

503 The practice of conducting FIH/early CTs with integrated protocols means that the information
504 generated in previous parts needs to be analysed and integrated into an assessment in a limited
505 timeframe as defined in the protocol prior to making a decision on proceeding to the next part.

506 Within an integrated protocol all parts need to be predefined, including possible modifications, with
507 specification on the basis of existing data and information, e.g. all non-clinical and, if available, clinical
508 data. Any changes outside the predefined criteria should be communicated to the competent
509 authority(ies) and ethics committee(s), as applicable. For decision making see section 8.3.

510 Regarding the time sequence for the conduct of different parts, the following recommendations apply:

- 511 • A certain overlap of SAD and MAD parts may be considered acceptable. However, any overlap
512 should be scientifically justified and supported by a decision-tree and a review of the available
513 data before deciding on starting the MAD part.
- 514 • Other single dose parts (e.g. food interaction (FI)) could be conducted in parallel to the SAD part
515 provided the dose chosen and the expected exposure are equal to or lower than that which was
516 reached in a concluded preceding SAD cohort where all relevant data has been reviewed and no
517 dose escalation stopping criteria were met.
- 518 • Other study parts that involve multiple dosing (e.g. FI and drug-drug interaction) should not
519 overlap with any earlier SAD or MAD cohorts. All relevant SAD and MAD data should be reviewed
520 before starting these parts. Deviation from this should always be justified in the protocol.

521 **8.2.3. Choice of subjects**

522 The decision to conduct a study in healthy volunteers or patients should be scientifically justified.

523 Factors to consider include:

- 524 • the known risks inherent in the type of IMP;
- 525 • the molecular target;
- 526 • any long lasting or irreversible pharmacological effect;
- 527 • any immediate and potential long term toxicity;
- 528 • the relevance of the non-clinical safety testing;
- 529 • the relative presence of the target in healthy subjects or in patients; e.g. cancer patients;
- 530 • the possible higher variability in patients;
- 531 • the potential pharmacogenomic differences between the targeted patient group and healthy
532 subjects;
- 533 • possible interactions with subject's lifestyle, e.g. smoking, use of alcohol or drugs, excessive
534 exercise;
- 535 • the use of other medications with the possibility for adverse reactions and/or difficulties in the
536 interpretation of results;
- 537 • the patients' ability to benefit from other products or interventions;
- 538 • the predicted therapeutic window of the IMP;
- 539 • concomitant exposure of subjects to IMPs across trials. To alert to this, consideration may be
540 given to trial sites participation in e.g. national initiatives to prevent over-volunteering, where
541 available.

542 The key inclusion and exclusion criteria for trials involving healthy participants should also be in line
543 with normal ranges of vital signs (including ECG) and safety laboratory values.

544 **8.2.4. Subject assessments and interventions**

545 The subject safety assessments that will be routinely conducted and any additional monitoring actions
546 should be pre-specified and justified in line with the known non-clinical and pharmacological profile.
547 There should also be routine general monitoring to detect potential unexpected adverse effects that
548 are not related to known properties of the IMP (e.g. vital signs, ECG, respiratory signs and symptoms,
549 clinical lab values or general neurological assessment, physical examination and interview). Repeated
550 assessments, integrating all available pharmacological, PK, PD and toxicological knowledge, and rapid
551 processing of this information are crucial for the recognition and interpretation of developing toxicity at
552 an early or potentially reversible stage.

553 All planned assessments and interventions, for example clinical chemistry or radiological assessments,
554 should be clearly pre-specified. The exact nature of the assessments, and their timing should be
555 provided. Any subsequent proposal to omit an assessment should be justified, such as if a finding in
556 non-clinical data is shown to be animal specific.

557 Follow-up of subjects should be specified within the protocol (e.g. for possible delayed adverse
558 reactions). The sponsor should justify how safety monitoring should be extended for healthy volunteers
559 until parameters return to within the normal range or to baseline. Other examples of when extended
560 monitoring should be considered include when the mechanism entails enzyme inhibition (monitoring
561 should continue until enzyme activity has returned back to baseline or to an acceptable percentage of

562 baseline) or when prolonged PD effects are observed regardless of duration of target inhibition or PK
563 profile of the IMP.

564 **8.2.5. General considerations for all cohorts**

565 The number of subjects per dose increment (the cohort size) depends on the variability of both PK and
566 PD parameters and the trial objectives such as justifying progression to the next cohort.

567 A maximum number of cohorts that will be dosed and the corresponding doses with the expected
568 exposure for each cohort should be stated in the protocol.

569 Flexibility can be allowed for the number of cohorts to be investigated but any plan to include optional
570 additional cohorts should be clearly pre-defined and the underlying rationale provided.

571 It is not acceptable to allow repetition of a dose level or cohort where that dose has met any of the
572 dose escalation stopping rules (see section 8.2.10.). If repetition of cohorts is allowed in the protocol
573 then only a lower or intermediate dose level would be acceptable and this should be clearly indicated.

574 **8.2.6. Precautions to apply between treating subjects within a cohort**

575 It is considered appropriate to design the administration of the first dose in any cohort so that a single
576 subject receives a single dose of the active IMP. When the study design includes the use of placebo it
577 would be appropriate to allow for one subject on active and one on placebo to be dosed simultaneously
578 prior to dosing the remaining subjects in the cohort.

579 There should be an adequate period of time between the administration of treatment to these first
580 subjects in a cohort and the remaining subjects in the cohort to observe for any reactions and adverse
581 events. The duration of the interval of observation should be justified and will depend on the properties
582 of the IMP and the interpretation of the available data, including non-clinical PK and PD. Experience
583 and identified risk factors from CTs with comparable IMPs/medicinal products should also be
584 considered. At the end of the observation period there should be a clearly defined review of all data
585 before allowing dosing of further subjects in the cohort, in the same manner as the precautions applied
586 between cohorts (see section 8.2.7) and there should be dose stopping rules in place to prevent
587 further dosing if any rule is met (see also section 8.2.10). In the event of any serious adverse reaction,
588 further administration of the IMP to subjects should be immediately stopped, so that further subjects
589 in the cohort are not exposed.

590 This approach may also be appropriate at later stages of study design, e.g. on the steep part of the
591 dose response curve, when approaching target saturation levels or exposure margins to non-clinical
592 NOAELs, in case of non-linear PK, or in light of emerging clinical signs or adverse events that do not
593 meet stopping criteria.

594 **8.2.7. Precautions to apply between cohorts**

595 Administration in the next cohort should not occur before participants in the previous cohort have been
596 treated and PK data, where available, or possible AEs from those participants are reviewed in
597 accordance with the protocol. Thus all relevant data from cohort "n" should be reviewed prior to
598 allowing dosing of cohort "n+1". Review of all previous cohorts' data in a cumulative manner is
599 preferred. Late emerging safety issues that may have occurred after the time-point for the dose
600 escalation decision (e.g. 48h safety data for each subject set as the minimum data required but
601 significant event(s) happening at 7 days post dose) can then be considered.

602 All emerging PD, PK and safety data should be critically reviewed against the pre-defined stopping
603 criteria (see section 8.2.10), including exposure limits that are not to be exceeded. Account should be
604 taken of any signs related to potential PD or toxicity targets identified in non-clinical studies. While
605 there can be no delay for safety data, a lack of PD information or a reduced PK data set could be
606 justifiable in some cases, such as a short duration of the PD effect.

607 The review should include comparison of PK, PD or PK/PD data from any previous cohorts with known
608 non-clinical data and safety information to inform the decision, as well as comparison to any initial or
609 updated PK and/or PD modelling and simulation. The model and planned dose(s) should be adapted
610 accordingly, if needed. In addition, the review should consider whether adaptation of the protocol in
611 other areas is required to ensure continuing safety of trial participants, such as safety monitoring
612 parameters and timings or length of the follow-up period. In specific situations where PK, PK/PD
613 models are of limited value (e.g. signs of dissociation between PK and PD profiles and potential
614 toxicities due to off-target effects at the administered human doses) dose escalation schemes and
615 progression to further study parts need to be more cautious (e.g. consider a slower progression of the
616 dose escalation scheme).

617 Unanticipated responses may require a revised dose escalation. Conversely, since the initial doses may
618 be very low, it is anticipated that early cohorts may not show any pharmacological effects.

619 Time intervals between cohorts should be guided by non-clinical and clinical PK and PD data and, if
620 appropriate, by data from comparable (investigational) medicinal products. The time interval should be
621 stated in the protocol. Flexibility to allow for a defined longer review time in the event of emerging
622 data could be accepted, but shortening of the review time for any dose escalation should always
623 require a substantial amendment.

624 The same principles apply when detailing the review between different parts of the study.

625 **8.2.8. Precautions to apply between study parts**

626 In general, the same approach as between cohorts applies (see previous section 8.2.7.), including
627 review of all previous finished study parts and cohorts data in a cumulative manner (PK, PD, safety)
628 and including late emerging information. The actual data need to be compared to the initial simulated
629 expectations and refined in line with available clinical information. The planned dose(s) should be
630 adapted accordingly, if needed.

631 Prior to any further part following (or overlapping with) the SAD part, sufficient information should be
632 available from completed preceding parts or/and cohorts to ensure safety of selected dose/exposure
633 prior decision to start the part.

634 For studies with multiple parts, consideration may be given to submitting an interim report to the
635 competent authorities for review as a substantial amendment prior to the start of further dosing
636 phases.

637 **8.2.9. Dose escalation scheme**

638 The amount of data required in the review prior to allowing dose escalation or beginning of a new
639 study part – in alignment with the predefined criteria in the protocol – is key and the following are
640 regarded as minimum criteria to include in the protocol:

- 641 • 'Evaluable' subjects should be defined and it is expected that these are subjects who have
642 completed all planned study visits.

643 • Data collection from all subjects in a given dosing cohort should be complete to proceed to the
644 next dose cohort. When it is considered that not all subjects in a cohort may meet the definition
645 of “evaluable”, the protocol should clearly define the minimum number of evaluable subjects
646 required for review. This number should be adequate for data review and reliable decision-
647 making.

648 • Subjects who have discontinued for any reason should also be considered in the relevant
649 component of data review.

650 All data (e.g. safety, PK and any other available information, such as PD) for the evaluable subjects
651 should be considered for review.

652 **8.2.10. Stopping rules**

653 The protocol should define unambiguous stopping rules which result in an immediate stop to dosing. It
654 should further be specified in the rule if it implies a final end of dosing or a possible temporary halt
655 with dosing re-starting after a full evaluation of available data and the approval of a substantial
656 amendment. The submitted substantial amendment should include a justification of the proposed
657 dosing for the continuation of the trial and details of any adjustments to the protocol including
658 additional safety monitoring, if applicable.

659 Stopping rules should be defined for each of the following:

- 660 • final stop to dosing and termination of the trial;
- 661 • stopping for an individual subject, at any time in the trial;
- 662 • stopping within a cohort
 - 663 – when allowing remaining subjects in a cohort to be dosed after the preceding subjects have
664 completed the first dosing period;
 - 665 – during multiple dosing;
- 666 • progression to the next part of the trial;
- 667 • any dose escalation parts of the trial.

668 Separate criteria can be in place for each of the above, or it may be appropriate to use the same
669 criteria for several areas of the protocol. For example, stopping rules for dose escalation could be the
670 same as those for within a cohort or those for individual subjects. Integrated protocols should clearly
671 outline decision points for situation where stopping rules are met.

672 Stopping rules for healthy volunteer trials should include:

- 673 • a ‘serious’ adverse reaction (AR) (i.e. a serious adverse event (AE) considered at least possibly
674 related to the IMP administration) in one subject;
- 675 • ‘severe’ non-serious ARs (i.e. severe non-serious AEs considered as, at least, possibly related to
676 the IMP administration) in two subjects in the same cohort.

677 Consideration should be given to stopping criteria based on a rolling review of the data that takes
678 account of ‘moderate’ non-serious ARs (i.e. moderate AEs at least possibly related to the IMP
679 administration) and their relation to PD effects, the number of subjects in which they occur,
680 concurrency of more than one within the same subject and potential safety signals identified for other

681 IMPs in the same class. In patients, changes from baseline measurements should also be considered,
682 and not just absolute criteria based on upper limits of normal that might apply for healthy volunteers.

683 A dose stopping criterion of the clinical exposure (C_{max} or AUC) equivalent to the exposure achieved at
684 the NOAEL determined in the most sensitive non-clinical species, adjusted by safety factors if
685 appropriate and based on available PK data, should be included.

686 Comparisons of the non-clinical and clinical exposure should be based on the maximum clinical
687 exposure in an individual subject within a cohort and not mean (average) clinical exposure in a
688 cohort.

689 Consideration should also be given to the addition of stopping rules based on toxicity seen in animals,
690 particularly if monitoring of toxicities is feasible in the clinic, e.g. if the toxicity is reversible, or linked
691 to the mode of action or a putative target.

692 Additional stopping rules should also be based on what is known about the PD of the drug (e.g. mode
693 of action, chemical structure and others compounds in class or other classes).

694 **8.2.11. Monitoring and communication of adverse events/reactions**

695 All clinical staff should be trained to identify those reactions and how to respond to those or any other
696 adverse events or reactions. Rapid access to the treatment allocation codes should be constantly
697 available, where relevant. It is therefore imperative that in any double-blind study design there are
698 clear instructions in the protocol for unblinding in the case of an emergency.

699 In cases where there is a risk of a certain type of adverse reaction occurring in humans, a treatment
700 strategy should be described in the protocol. This should include the availability of specific antidotes
701 where they exist and a clear plan of availability of supportive treatment emergency facilities and
702 medical staff.

703 The length of the monitoring period and the nature of monitoring within, and if deemed appropriate
704 outside, the research site should be justified.

705 Of high importance in the protocol is a prompt communication plan for SAEs and suspected unexpected
706 serious adverse reactions (SUSARs) or serious safety-related protocol deviations between the sponsor,
707 all study sites and investigators and trial subjects. It is particularly important in the case of multicentre
708 trials to clearly define the processes for communication of safety data or rapid implementation of
709 corrective or preventive actions between the sponsor and all study sites and investigators and trial
710 subjects.

711 Sponsors should ensure that processes are in place, before the trial starts, for expedited reporting of
712 any SUSARs to the Member States concerned (MSC) (competent authority(ies)/ethics committee(s)),
713 to the investigator(s) and to the EudraVigilance Clinical Trial Module.

714 In the case of emerging safety issues, investigators and participants (at any site) are to be informed as
715 soon as possible, and at least prior to any planned next dosing in multiple part or sentinel design. Any
716 SUSAR in a healthy volunteer should be also reported to the MSC without undue delay.

717 **8.3. Documentation of sponsor and investigators responsibilities**

718 The responsibilities of the sponsor and investigator(s) (as well as any other experts or study staff) in
719 decision making and the timing of any decisions should be clearly defined in the protocol.

720 Responsibility with regard to breaking the treatment code in emergency situations should also be

721 documented. It is also the case that unblinding in an emergency may be needed without involvement
722 of the monitor or sponsor.

723 The composition of any decision making group or committee should be documented in the protocol so
724 that their appropriateness to participate in the monitoring and decision-making can be established.
725 Other details to include are the exact remit of the group and the roles of all members in the committee
726 or in relation to the sponsor. The members of the group should also be sufficiently independent from
727 IMP administration and monitoring.

728 **8.4. Investigator site facilities and personnel**

729 FIH/early CTs should take place in appropriate clinical facilities and be conducted by trained
730 investigators who have acquired the necessary expertise and experience in conducting early phase
731 trials and medical staff with appropriate level of training and previous experience of early phase trials.
732 The training should include, as an example, relevant medical expertise and GCP training. They should
733 also understand specific characteristics of the IMP, and of its target and mode of action.

734 FIH/early CTs should take place under controlled conditions (e.g. hospitalisation), with the possibility
735 of close supervision of study subjects during and after dosing as required by the protocol. Units should
736 have immediate access to equipment and appropriately qualified staff for resuscitating and stabilising
737 individuals in an acute emergency (such as cardiac emergencies, anaphylaxis, cytokine release
738 syndrome, convulsions, hypotension), and ready availability of intensive care unit facilities. Procedures
739 should be established between the clinical research unit and its nearby intensive care unit regarding
740 the responsibilities and undertakings of each in the transfer and care of patients. All FIH/early CTs for
741 an IMP should preferably be conducted at a single site (to gather collective experience). When different
742 sites are involved, this should be justified.

743 **Abbreviations**

744 AE - Adverse event

745 AR - Adverse reaction

746 ATD - Anticipated therapeutic dose

747 AUC - Area under the curve

748 CHMP - Committee for Medicinal Products for Human Use

749 C_{max} - Maximum concentration

750 CT - Clinical trial

751 CTA - Clinical trial application

752 CTFG - Clinical Trial Facilitation Group

753 CTR - Clinical Trial Regulation

754 ECG - Electrocardiogram

755 FI - Food interaction

756 FIH - First-in-human

757 GCP - Good Clinical Practice

758	GLP - Good Laboratory Practice
759	IB - Investigator's Brochure
760	ICH - International Conference on Harmonisation
761	IMP - Investigational medicinal product
762	MABEL - Minimal anticipated biological effect level
763	MAD - Multiple ascending dose
764	MSC - Member State concerned
765	MTD - Maximum tolerated dose
766	NOAEL - No observed adverse effect level
767	PAD - Pharmacologically active dose
768	PBPK - Physiologically-based pharmacokinetic
769	PD - Pharmacodynamic
770	PK - Pharmacokinetic
771	PoC - Proof of concept
772	PoP - Proof of principle
773	SAD - Single ascending dose
774	SAE - Serious adverse event
775	SUSAR - Suspected unexpected serious adverse reaction
776	TK - Toxicokinetic