



**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE  
(CHMP)**

*DRAFT*

**GUIDELINE ON REQUIREMENTS FOR FIRST-IN-MAN CLINICAL TRIALS FOR  
POTENTIAL HIGH-RISK MEDICINAL PRODUCTS**

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**KEYWORDS**

<b>GUIDELINE ON REQUIREMENTS FOR FIRST-IN-MAN CLINICAL TRIALS FOR POTENTIAL HIGH-RISK MEDICINAL PRODUCTS</b>
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**TABLE OF CONTENTS**

<b>EXECUTIVE SUMMARY .....</b>	<b>3</b>
<b>1. INTRODUCTION.....</b>	<b>3</b>
<b>2. SCOPE.....</b>	<b>4</b>
<b>3. LEGAL BASIS .....</b>	<b>4</b>
<b>4. MAIN GUIDELINE TEXT .....</b>	<b>4</b>
4.1    DEFINITION OF POTENTIAL HIGH-RISK INVESTIGATIONAL MEDICINAL PRODUCTS.....	4
4.2    QUALITY ASPECTS.....	5
4.3    NON-CLINICAL REQUIREMENTS .....	5
4.3.1 <i>Pharmacodynamics</i> .....	6
4.3.2 <i>Pharmacokinetics</i> .....	6
4.3.3 <i>Demonstration of relevance of the animal model</i> .....	6
4.3.4 <i>Safety Pharmacology</i> .....	7
4.3.5 <i>Toxicology</i> .....	7
4.3.6 <i>Calculation of the first dose in man</i> .....	7
4.4    CLINICAL REQUIREMENTS.....	8
4.4.1 <i>General aspects</i> .....	8
4.4.2 <i>Protocol design</i> .....	8
4.4.2.1 <i>Choice of subjects for first-in-man trials with high-risk medicinal products</i> .....	8
4.4.2.2 <i>Route and rate of administration</i> .....	9
4.4.2.3 <i>Choice of the first dose in human</i> .....	9
4.4.2.4 <i>Precautions to apply between doses within a cohort</i> .....	9
4.4.2.5 <i>Precautions to apply between cohorts</i> .....	9
4.4.2.6 <i>Dose escalation scheme</i> .....	9
4.4.2.7 <i>Stopping rules and decision making</i> .....	9
4.4.2.8 <i>Monitoring for adverse events/reactions</i> .....	9
4.4.3 <i>Site of the clinical trial</i> .....	10
<b>REFERENCES (SCIENTIFIC AND / OR LEGAL) .....</b>	<b>10</b>

## 1 EXECUTIVE SUMMARY

2 This guideline is intended to assist sponsors in the transition from non-clinical to early clinical  
3 development. It provides criteria to classify new investigational medicinal products as potential high-  
4 risk medicinal products. It also gives guidance on quality aspects, non-clinical testing strategies and  
5 designs for first-in-man clinical trials for high-risk medicinal products, including the calculation of the  
6 initial dose to be used in humans, the subsequent dose escalation and the management of risk.

### 7 1. INTRODUCTION

8 The safety of subjects participating in first in man studies is the paramount consideration in  
9 proceeding to clinical trials in man. Such subjects would not normally be expected to derive any  
10 therapeutic benefit.

11 Decisions on strategies for development of a new medicine and the experimental approaches used to  
12 assemble information relevant to the safety of first-in-man clinical trials must be science-based, made  
13 and justified on a case-by-case basis.

14 Quality requirements for high-risk medicinal products are not different to other medicinal products.  
15 Nevertheless, special consideration should be given to certain aspects.

16 The non-clinical testing and experimental approaches for first-in-man studies with potential high-risk  
17 investigational medicinal products<sup>1</sup> raise particular difficulties. For this type of product the ability of  
18 non-clinical studies to predict safety issues in humans may be reduced because the nature of the target  
19 is more specific to humans or because of other factors.

20 The factors influencing the decision to proceed with the trial in healthy volunteers or patients and how  
21 to conduct the trials need to be carefully considered. Attention should be given to the calculation of  
22 the initial dose to be used in humans and to the subsequent dose escalations, intervals between doses  
23 to different individuals and the management of risk.

24 In defining an appropriate early development programme for high-risk medicinal products,  
25 information needs to be integrated from many sources and frequently reviewed in an iterative process.  
26 This guideline is intended to assist Sponsors in the transition from non-clinical to early clinical  
27 development by outlining factors to be considered in the non-clinical testing strategy and designs of  
28 first -in -man clinical trials for high-risk medicinal products.

29 Expert scientific advice on this topic may be requested from the relevant Member State Competent  
30 Authorities or the EMA.

31 This guideline should be read especially in conjunction with the following guidelines (see also section  
32 references):

#### 33 *Non-clinical aspects:*

- 34 • Non-Clinical Safety Studies For The Conduct Of Human Clinical Trials For Pharmaceuticals  
35 [\(ICH M3\), CPMP/ICH/286/95,](#)
- 36 • Preclinical safety evaluation of biotechnology-derived pharmaceuticals [\(ICH S6\)](#)  
37 [CPMP/ICH/302/95,](#)
- 38 • The Non-clinical Evaluation of the Potential for delayed Ventricular Repolarization (QT  
39 Interval Prolongation) by Human Pharmaceuticals [\(ICH S7B\) CPMP/ICH/423/02](#)
- 40 • Safety pharmacology studies for human pharmaceuticals [\(ICH S7A\)- CPMP/ICH/539/00](#)

#### 41 *Quality aspects*

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<sup>1</sup> Throughout this guideline the term “high-risk medicinal product” will be used to refer to all investigational medicinal products that have a *potential* for high risk in first-in-man administration. (see section 4.1)

- 42 • [EUDRALEX -Volume 4](#) - Medicinal Products for Human and Veterinary Use: Good  
43 Manufacturing Practice. Annexe 13: Manufacture of Investigational Medicinal Products.
- 44 • Guideline on Virus Safety Evaluation of Biotechnological Investigational Medicinal Products  
45 - Draft- [EMA/CHMP/BWP/398498/2005-corr.](#)
- 46 • Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation  
47 concerning Investigational Medicinal Products in Clinical Trials. [CHMP/QWP/185401/2004](#)

#### 48 *Clinical aspects*

- 49 • Guideline for Good Clinical Practice ([ICH E6](#)), [CPMP/ICH/135/95](#)
- 50 • General Considerations for Clinical Trials, ([ICH E8](#)) [CPMP/ICH/291/95](#).
- 51 • [EUDRALEX- Vol 10](#) – [Clinical trials](#). In particular: Chapter I: Application and Application  
52 Form and Chapter II : Monitoring and Pharmacovigilance.

## 53 **2. SCOPE**

54 This guideline particularly refers to high-risk medicinal products, including chemical and biological  
55 medicinal products. It specifically covers the first administration of a single dose of a high-risk  
56 medicinal product and the initial single ascending dose phase of clinical development.

57 Gene and cell therapy medicinal products are excluded and are to be covered by specific guidelines.

## 58 **3. LEGAL BASIS**

59 This guideline applies to relevant Clinical Trial Authorisation applications submitted in accordance  
60 with Directive 2001/20/EC and should be read in conjunction with Directive 2001/83 as amended and  
61 its Annex I.

## 62 **4. MAIN GUIDELINE TEXT**

63 Sponsors should consider whether the criteria and guidance for high-risk medicinal products are  
64 applicable when planning a first-in-man clinical trial.

### 65 **4.1 Definition of potential high-risk investigational medicinal products**

66 Medicinal products are defined as potential high-risk medicinal products when there are concerns that  
67 serious adverse reactions in first-in-man clinical trials may occur. These concerns may be derived  
68 from particular knowledge or uncertainties on (1) the mode of action, and/or (2) the nature of the  
69 target, and/or (3) the relevance of animal models.

70 For many new medicinal products, the conventional non-clinical programme provides an acceptable  
71 safety estimate for a first administration in humans. However, for high-risk medicinal products this  
72 programme might not be sufficiently predictive of serious adverse reactions in man and their  
73 development programme might require special consideration. Transition from non-clinical to clinical  
74 testing therefore requires special precautions to minimise these risks.

75 The Sponsor should discuss the following criteria for all first-in-man trials in their clinical trial  
76 authorisation application. These criteria should be taken into account on a case-by-case basis when  
77 deciding whether or not a new medicinal product is of potential high-risk.

- 78 • Mode of action

79 Consideration should be given to the novelty, plausibility and extent of knowledge of the proposed  
80 mode of action. This includes the nature and intensity (extent, amplification, duration, reversibility) of  
81 the effect of the active substance on the target and the type of dose response (linear, non-linear,  
82 U-shaped, bell-shaped). Previous exposure of human beings to compounds that have related biological  
83 mechanisms should also be considered.

84 For example, the following mechanisms could be considered as high risk:

- 85 – A pleiotropic mechanism, e.g. leading to various physiological effects, or targets that are  
86 ubiquitously expressed, as often seen in the immune system,

87 – A mechanism that bypasses physiological control mechanisms, e.g. CD3 or CD28  
88 (supra-) agonists.  
89 sponsors should also discuss the novelty of the structure of the medicinal product, for example a new  
90 type of engineered structural format like bispecific antibodies or novel fusion proteins. Such products  
91 may be high-risk medicinal products even if the parent compounds are well established.

92 • Nature of the target

93 Irrespective of the mode of action, the nature of the target itself might impact on the risk inherent to a  
94 first administration to humans, and sponsors should discuss the following aspects accordingly:

- 95 – the extent of the knowledge on the structure, tissue distribution, cell specificity, disease  
96 specificity, regulation, and biological function of the human target including “down-stream”  
97 effects.
- 98 – the relationship between the biology of the target, and the physiological or pharmacological  
99 effects, in both normal and pathological states.

100 • Relevance of animal models

101 The Sponsor should compare the available animal species to humans taking into account the target, its  
102 structural homology, distribution, signal transduction pathways and the nature of pharmacological  
103 effects.

104 If available animal models are of limited relevance to study properly the pharmacological and  
105 toxicological effects of the medicinal product, it should be considered as high-risk.

106 **4.2 Quality aspects**

107 The requirements for high-risk medicinal products regarding the physico-chemical characterisation  
108 and, additionally biological characterisation of biological products, are not different from any  
109 medicinal products. Quality concerns alone should not qualify a product for being a high-risk  
110 medicinal product. However, quality attributes might add to the risks inherent for a first-in-man  
111 administration, e.g. due to insufficient knowledge for entirely novel types of medicinal products or for  
112 entirely novel types of manufacturing processes.

113 Specific points to be considered for high-risk medicinal products are:

114 • Characterisation

115 It is important to have reached a high degree of quality characterisation even at this early point of  
116 development. A characterisation of product-related variants, including heterogeneity and degradation  
117 products, that may have an impact on the pharmacological profile of the molecule should be  
118 performed. Special consideration should be given to the suitability and qualification of methods to  
119 sufficiently characterise the active substance and drug product.

120 • Determination of strength and potency

121 In order to determine a safe starting dose of a high-risk medicinal product, the methods used for  
122 determination of the strength and (where appropriate and possible) the potency of the product need to  
123 be relevant, reliable and qualified. As an example, where the dose is based on biological activity and is  
124 expressed in arbitrary units, and the assays are not qualified and/or validated to ensure the reliability,  
125 the doses given to animals may be poorly defined and mislead the interpretation of a safe dose. For a  
126 biological medicinal product, the lack of a potency assay measuring the expected in-vivo activity  
127 should be fully justified.

128 • Comparability with the material used in non-clinical studies

129 During the early development of a product, significant modifications to the manufacturing process  
130 frequently occur. Particularly in the case of complex molecules, these modifications can potentially  
131 result in subtle changes to the molecular structure that may not be detectable from characterisation  
132 studies but can affect binding characteristics and other biological properties and could have clinical  
133 consequences. Given the fact that major clinical decisions are based on the non-clinical data, it is  
134 important to show that the non-clinical data are still valid. Where there are differences and product  
135 characterisation cannot fully assure that the product is comparable, some further non-clinical studies  
136 may be needed with the product intended for use in the first-in-man trial.

137 • Reliability of very small doses  
138 Applicants should demonstrate that the intended formulation of the doses to be administered provides  
139 correct dosing. There is a risk of reduced accuracy in cases where the medicinal product needs to be  
140 diluted, to prepare very small doses, or the product is provided at very low concentrations, e.g. the  
141 product could be adsorbed to the wall of the container or infusion system. This might lead to an over-  
142 estimation of the safety of the initial clinical doses and non-clinical safety data.

### 143 4.3 Non-clinical requirements

#### 144 4.3.1 Pharmacodynamics

145 Pharmacodynamic studies should address the mode of action, and provide knowledge on the biology  
146 of the target. These data will help to characterise the pharmacological effects and to identify the most  
147 relevant animal model.

148 For high-risk medicinal products, it is particularly important to fully characterise the primary and  
149 secondary pharmacodynamics, in *in vitro* animal and human systems and *in vivo* in one or more  
150 chosen animal models. These studies should include receptor binding and occupancy, duration of  
151 effect and dose-response.

152 A dose-response curve of the pharmacological effect(s) should be established with sufficient titration  
153 steps in order to increase the likelihood to detect distinct pharmacological effects with low doses and  
154 to identify active substances with U-shaped or bell-shaped dose-response. Such distinct or even  
155 contrary effects have been reported with biologicals. Since a low dose is to be administered to humans  
156 in the first-in-man trial, this is of high importance.

157 Although GLP compliance is not mandatory for pharmacodynamic and pharmacokinetic studies, they  
158 should be of high quality and consistent with the principles of GLP.

#### 159 4.3.2 Pharmacokinetics

160 In addition to standard absorption, distribution, metabolism and elimination (ADME) requirements  
161 (see ICH S3, S6), which should be available in all species used for *in vivo* studies, exposures at  
162 pharmacological doses in the relevant animal models should be determined.

#### 163 4.3.3 Demonstration of relevance of the animal model

164 Qualitative and quantitative differences may exist in biological responses in animals compared to  
165 humans. For example, there might be differences in affinity for molecular targets, tissue distribution of  
166 the molecular target, cellular consequences of target binding, cellular regulatory mechanisms,  
167 metabolic pathways, or compensatory responses to an initial physiological perturbation.

168 Where there is evidence of species-specificity of action from *in vitro* studies with human cells  
169 compared with cells from a test species, the value of the *in vivo* response of the test species may be  
170 significantly reduced in terms of predicting the *in vivo* human response. It should be noted that a  
171 similar response in human and animal cells *in vitro* is not necessarily a guarantee that the *in vivo*  
172 response will be similar.

173 In practice this means that non-clinical animal studies with highly species-specific medicinal products  
174 may:

- 175 • not reproduce the intended pharmacological effect in humans;
- 176 • give rise to misinterpretation of pharmacokinetic results;
- 177 • not identify relevant toxic effects.

178 It should be noted that human specific proteins are likely to be immunogenic in animal species.  
179 Therefore repeat dosing studies in animals may not predict the effects of such substances in humans.  
180 High species-specificity of a medicinal product makes the non-clinical evaluation of the risk to  
181 humans much more difficult, but does not imply that there is always an increased risk in first-in-man  
182 trials. In any case, a highly cautious approach is needed.

183 The demonstration of relevance includes:

- 184       ○ Comparison of pharmacodynamics
- 185             • Receptor structure, binding, occupancy and functional consequences, including cell
- 186             signalling if relevant. A high degree of homology of structure of the target does not
- 187             necessarily imply a comparable pharmacological effect;
- 188             • Data on the functionality of additional functional domains, if applicable, e.g. Fc
- 189             receptor system for monoclonal antibodies.
- 190       ○ Comparison of pharmacokinetics.
- 191       ○ Cross-reactivity studies using human and animal tissues.

192 Where no relevant species exists, the use of relevant transgenic animals expressing the human receptor

193 or the use of homologous proteins is strongly recommended.

194 The search for a relevant animal model should be documented and justified in detail.

#### 195 4.3.4 Safety Pharmacology

196 In addition to the core battery outlined in the CHMP/ICH guidelines S7A and S7B, for high risk

197 medicinal products, additional studies to investigate effects in other organ systems should be carried

198 out on a case by case basis. In particular, for medicinal products targeting the immune system,

199 potential unintended effects should be investigated, e.g. using *in vitro* studies, including human

200 material.

#### 201 4.3.5 Toxicology

202 The toxicology programme should be performed in appropriate animal species and include toxico-

203 kinetics. The inclusion of relevant pharmacodynamic endpoints should be considered, where possible.

204 Toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged. When

205 using a homologous or transgenic model approach, the information gained is optimised when the

206 interaction of the product and the target receptor has similar physiological consequences to those

207 expected in humans.

208 Animal models that are thought to be similar to the human disease may provide further insight in the

209 pharmacological action, the pharmacokinetics, and dosing in patients. They may also be useful in the

210 determination of safety (e.g., evaluation of undesirable promotion of disease progression). In certain

211 cases, studies performed in animal models of disease may be used as an acceptable alternative to

212 toxicity studies in normal animals. The scientific justification for the use of these animal models of

213 disease to support safety should be provided.

#### 214 4.3.6 Calculation of the first dose in man

215 In general, the calculation of the first dose in man is based on No Observed Adverse Effect Level

216 (NOAEL) determined in non-clinical safety studies performed in the most sensitive and relevant

217 animal species, adjusted with allometric factors or on the basis of pharmacokinetics. The relevant dose

218 is then reduced/adjusted by appropriate safety factors according to the particular aspects of the

219 molecule and the design of the clinical trials.

220 For high-risk medicinal products, an additional approach to dose calculation should be taken. The use

221 of 'Minimal Anticipated Biological Effect Level' (MABEL) approach is recommended. The MABEL

222 is the anticipated dose level leading to a minimal biological effect level in *humans*. Safety factors are

223 usually applied for the calculation of the first dose in man from MABEL.

224 The calculation of MABEL should utilise all relevant *in vitro* and *in vivo* available information from

225 pharmacodynamic/pharmacokinetic data such as:

- 226       i) receptor binding and receptor occupancy studies *in vitro* in target cells from human and the
- 227       relevant animal(s) species and *in vivo* in the relevant animal species;
- 228
- 229       ii) concentration-response curves *in vitro* in target cells from human and the relevant animal(s)
- 230       species and dose response *in vivo* in the relevant animal species.
- 231
- 232       iii) exposures at pharmacological doses in the relevant species.

233 The above data should be integrated in a PK/PD modelling approach for the determination of the

234 MABEL.

235 In order to further limit the potential for adverse reactions in humans, safety factors should be applied  
236 in the calculation of the first dose in man from the MABEL. These should take into account criteria of  
237 risks such as the novelty of the active substance, its biological potency and its mode of action, the  
238 degree of species specificity, and the shape of the dose-response curve. The safety factors used should  
239 be justified.

240 When the methods of calculation (e.g. NOAEL, MABEL) give different estimations of the first dose  
241 in man, the lowest value should be used.

## 242 **4.4 Clinical requirements**

### 243 *4.4.1 General aspects*

244 The safety of participants in first-in-man clinical trials with high-risk medicinal products can be  
245 enhanced by careful consideration of the risks associated with a trial and by managing those risks as  
246 part of the design of the trial. To identify those risks several key aspects of the trial design should be  
247 evaluated and guide the choice of:

- 248 • study population;
- 249 • first dose;
- 250 • number of subjects per dose increment (cohort);
- 251 • interval between dosing subjects within the same cohort;
- 252 • dose escalation increments;
- 253 • transition to next dose cohort;
- 254 • stopping rules;
- 255 • defining responsibilities for decisions with respect to subject dosing and dose escalation.

256 In general, the higher the potential risk associated with the type of medicinal product and its  
257 pharmacological target, the greater the precautionary measures that should be exercised in the design  
258 of the first-in-man study. The protocol should describe the strategy for managing risk including a plan  
259 for monitoring safety and managing of any adverse reactions and the use of an independent safety  
260 monitoring board.

261 It is recognised that the design of Phase I studies often include subjects receiving placebo. In such  
262 cases it will be important that any decisions taken with respect to subsequent dosing at the same dose  
263 level and or dose escalation, take into account the number of subjects that might have received the  
264 active medicinal product. The study design including randomisation schemes should take this into  
265 account.

### 266 *4.4.2 Protocol design*

#### 267 *4.4.2.1 Choice of subjects for first-in-man trials with high-risk medicinal products*

268 One of the main purposes of a first-in-man trial is to assess tolerance and subjects are not generally  
269 expected to derive any therapeutic benefit. The paramount factors should always be the safety, rights  
270 and well-being of the volunteers, whether patients or healthy individuals, and the value of what can be  
271 learned from the clinical trial.

272 The choice of the study population for high-risk medicinal products, i.e. healthy subjects or patients,  
273 should be fully justified by the Sponsor on a case-by-case basis. Several factors should be considered,  
274 such as (a) the risks inherent in the type of medicinal product, (b) its molecular target (c) immediate  
275 and potential long term toxicity, (d) the presence of the target in healthy subjects or in patients only  
276 and (e) the possible higher variability in patients. Concurrent medication in patients may give rise to  
277 the potential for interactions with the possibility for adverse reactions and/or difficulties in the  
278 interpretation of results. The Sponsor should also consider whether any effects that may be seen in the  
279 population of choice are indeed relevant and can be extrapolated to the intended clinical application.  
280 Special considerations should be given to potential long-term consequences on physiological systems  
281 and potential long-term safety problems.

282 Healthy subjects or patients included in first-in-man clinical trials must not be simultaneously in  
283 another clinical trial. It is important to include clear exclusion criteria to prevent concomitant exposure  
284 to investigational medicinal products.

285 *4.4.2.2 Route and rate of administration*

286 Careful consideration should be given to the choice of route of administration and the rate of  
287 administration with careful monitoring for an adverse reaction or exaggerated response. In the case of  
288 an intravenous administration, a slow infusion over several hours may be more appropriate than a slow  
289 bolus over several minutes. This would allow monitoring for an adverse reaction and if clinically  
290 indicated, timely discontinuation of the infusion in order to prevent a serious outcome.

291 *4.4.2.3 Choice of the first dose in human*

292 The calculation of the first dose in humans has been discussed above in detail (see section 4.3.6).

293 *4.4.2.4 Precautions to apply between doses within a cohort*

294 For trials with high-risk medicinal products, an initial sequential dose administration design should be  
295 employed within each cohort in order to minimise any risks. Any non-sequential dose administration  
296 within each cohort should be justified. There must be an adequate period of observation between first,  
297 second, and subsequent administrations, depending on the properties of the product, the data available  
298 including non-clinical PK and PD data, if available already existing experience with comparable  
299 medicinal products and identified risk factors. The duration of the interval of observation should be  
300 fully justified.

301 The number of subjects per dose increment (the cohort size) depends on the trial objectives and the  
302 variability of both pharmacokinetic and pharmacodynamic parameters. While larger cohorts are likely  
303 to provide more precise data, they may not be necessary to fulfil the objectives of the study and could  
304 increase the complexity and time of a clinical development programme.

305 *4.4.2.5 Precautions to apply between cohorts*

306 For further cohorts, all the results from all subjects of the first cohort (and of subsequent cohorts) need  
307 to be carefully considered before administration of the first dose of the next cohort. In addition, any  
308 PK and PD data from the previous cohorts should be compared to known non-clinical  
309 pharmacokinetic, pharmacodynamic and safety information. In addition, any observed responses  
310 should be compared to the responses that were anticipated. Unanticipated responses may require a  
311 revised dose escalation. Administration in the next cohort should not occur before all the participants  
312 in the previous cohort have been treated and data/results from these participants reviewed.

313 Time intervals between doses between cohorts should be guided by existing non-clinical and clinical  
314 PK and PD data and if available, already existing experience with comparable medicinal products.

315 *4.4.2.6 Dose escalation scheme*

316 For dose escalation methodology, pharmacodynamic aspects including the shape of dose-response  
317 curve from non-clinical studies should be taken into account. Further dose increases should proceed  
318 with caution because the initial dose would have been low and there may be a steep dose-response  
319 curve.

320 The dose/toxicity or dose/effect relation observed in non-clinical studies, depending on which is  
321 steeper, should guide the dose increment between two dose levels. The steeper the increase in the  
322 dose/toxicity or dose/effect curves, the lower the dose increment that should be selected. The choice of  
323 the next dose level should include some estimate of the potential pharmacodynamic effects and  
324 adverse effects (if any). Information on exposure, effect, and safety from the preceding dose in human  
325 should be taken into account.

326 *4.4.2.7 Stopping rules and decision making*

327 The protocol should define stopping rules for the individual subject, cohort and trial. Sponsors should  
328 consider the use of an Independent Drug Safety Monitoring Board (IDSMB) and if this is not  
329 considered appropriate, this should be justified. The protocol should in any case define clear processes  
330 and responsibilities for making decisions about dosing of subjects and dose escalation.

331 *4.4.2.8 Monitoring for adverse events/reactions*

332 The trial design should provide a specific plan for monitoring for adverse events or adverse reactions.  
333 The mode of action of the high-risk medicinal product and any anticipated responses should be used to

334 identify likely adverse reactions. All clinical trial staff should be trained to identify those reactions and  
335 how to respond to those or any other adverse events or reactions.

336 In cases where there is a predictable risk of a certain type of severe adverse reaction occurring in  
337 humans, a treatment strategy should be described in the protocol. This should include the availability  
338 of specific antidotes where they exist and a clear plan of supportive treatment. There should be rapid  
339 access to the treatment allocation codes when relevant.

340 Communication of serious adverse experiences and suspected unexpected serious adverse reactions,  
341 SUSARs, is particularly important. Sponsors should ensure that processes are in place, before the trial  
342 starts, for expedited reporting of any SUSARs to the national competent authority (ies), ethics  
343 committee(s) and investigator(s). The sponsor needs to ensure that these processes include the  
344 necessary steps for reporting of the SUSARs to the EudraVigilance Clinical Trial Module.(see  
345 Directive 2001/20/EC and Chapter II of Volume 10 of the Rules Governing Medicinal Products in the  
346 European Community)

#### 347 Long term monitoring

348 Special considerations should be given to potential long-term consequences on physiological systems  
349 and potential long-term safety problems. The length of the monitoring period within and outside the  
350 research site should be justified as part of the strategy to manage risks in the clinical trial. For  
351 example, high-risk medicinal products that may have the potential to alter the immune system for long  
352 periods and/or may cause delayed unexpected adverse reactions such as infections or malignancies. In  
353 these circumstances, it may be necessary to implement long-term follow-up for the participants after  
354 finalisation of the study.

#### 355 4.4.3 Site of the clinical trial

356 First-in-man trials with high-risk medicinal products should take place in appropriate clinical facilities  
357 and be conducted by medical staff with appropriate level of training and expertise and an  
358 understanding of the investigational medicinal product, its target and mechanism of action. There  
359 should be immediate access to facilities for the treatment of medical emergencies (such as cardiac  
360 emergencies, anaphylaxis, cytokine release syndrome, convulsions, hypotension), facilities for  
361 stabilising individuals in an acute emergency and ready availability of Intensive Care Unit facilities.  
362 First-in-man single dose escalation trials for high-risk medicinal products should preferably be  
363 conducted as a single protocol at a single site, as this helps to assure the well-being of all trial  
364 participants particularly if new safety findings are identified. If several sites are planned for the study,  
365 this should be justified and an adequate information communication system between sites should be  
366 described.

## 367 **REFERENCES** (scientific and legal)

### 368 *Legal basis*

- 369 • [Directive 2001/20/EC](#) of the European Parliament and of the Council of 4 April 2001 on the  
370 approximation of the laws, regulations and administrative provisions of the Member States  
371 relating to the implementation of good clinical practice in the conduct of clinical trials on  
372 medicinal products for human use (*Official Journal L 121, 1/5/2001 p. 34 - 44*).
- 373 • [Directive 2001/83/EC](#) of the European Parliament and of the Council of 6 November 2001 on the  
374 Community code relating to medicinal products for human use (*Official Journal L 311,*  
375 *28/11/2001 p. 67 - 128*).
- 376 Consolidated Directive 2001/83/EC of the European Parliament and of the Council of 6 November  
377 2001 on the Community code relating to medicinal products for human use as amended by  
378 Directive 2002/98/EC, Directive 2004/24/EC and Directive 2004/27/EC. (*Official journal l – 311,*  
379 *28/11/2004, p. 67 – 128*)
- 380 • Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for  
381 human use to the competent authorities, notification of substantial amendments and declaration of  
382 the end of the trial. [October 2005 Revision 2](#)

383 *Detailed guidances in Volume 10 of the Rules Governing Medicinal Products in the European*  
384 *Community*

- 385 • Detailed guidance on the application format and documentation to be submitted in an application  
386 for an Ethics Committee opinion on the clinical trial on medicinal products for human use  
387 [February 2006 Revision 1](#)
- 388 • Detailed guidance on the collection, verification and presentation of adverse reaction reports  
389 arising from clinical trials on medicinal products for human use April 2006 [Revision 2](#).
- 390 • Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions  
391 (Eudravigilance – Clinical Trial Module) as required by Article 11, Article 17 and Article 18 of  
392 Directive 2001/20/EC [Revision 1](#). April 2004.