



**SUBMISSION OF COMMENTS ON  
GUIDELINE ON REQUIREMENTS FOR FIRST IN MAN CLINICAL TRIALS FOR POTENTIAL HIGH RISK MEDICINAL PRODUCTS  
(EMA/CHMP/SWP28367/2007)**

**COMMENTS FROM EFGCP, the EUROPEAN FORUM FOR GOOD CLINICAL PRACTICE**

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**GENERAL COMMENTS**

EFGCP is impressed with the quality of this draft guideline as a thorough reflection of most of the published recommendations made after the TGN 1412 event are integrated in this document (precautions to apply between doses/ cohorts, dose escalation scheme, stopping rule, etc...). However the introduction lacks concrete examples of what did go wrong in past examples, with references to the literature description of the cases. There are not too many cases (the Northwick Park Phase I unit in 2006, the SFBC unit in Miami, Florida in 2005, the death of a volunteer in Dublin in 1985, etc.). The EMA experts should agree about the reasons of each case and then verify that the Guideline addresses these issues effectively. Most of the recommendations in these guidelines would not have prevented the cases, and therefore there is a risk that by not ranking the proposed measures in order of priority as a function of dramas of the past, the Guideline only stifles translational research, as described in the specific comments section below.

However, EFGCP wants to emphasize that - as the safety of participants in first-in-human trials and the ethical aspects in this stage of drug development are of their great concern – a stronger representation of these aspects should be included in this document. This guideline concentrates very much on the scientific and technical aspects of FiM trials but does not sufficiently consider ethical aspects like information to subjects, indemnity coverage requirements and medical safe-guards during and after the study performance. For example, with regard to paragraph 4.4. Clinical Requirements, some more guidance should be given in terms of qualifications/certification of investigators and site personnel (see below specific comments). At several occasions it is too often referred to as ‘appropriate’ (appropriate training, appropriate facilities). In our opinion a Phase I unit should be able to anticipate each type of life threatening events. The conceptual issue is that adequate therapeutic facilities should immediately be available. We are also very much concerned that the required level of experience and qualification of investigators responsible for FiM trials are not specified in the guideline. Considerations should be given to the request for a training programme (with diploma) for Phase I investigators, the establishment of qualification checklists for ethics committees’ review of the facility and investigator suitability and an accreditation system for Phase I units.

In general EFGCP underlines the importance of this guideline document in order to move from the non-clinical testing to early clinical development.

**SPECIFIC COMMENTS ON TEXT**

| <b>GUIDELINE SECTION TITLE</b>               |  |  |
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| <b>Line no<sup>1</sup> . + paragraph no.</b> | <b>Comment and Rationale</b>   | <b>Proposed change (if applicable)</b>   |
| Executive Summary<br>6                       | This guideline should not only cover pharmacological, toxicological, quality and scientific aspects but put an equal emphasis on subject protection and clinical requirements. The following aspects should in principle be added: | ...the subsequent dose escalation, the management of risk <i>as well as the safeguard and protection of study participants, the suitability of clinical research units and the qualification of the clinical staff.</i>  |
| 1.<br>Introduction<br>9                      | In FiM trials there is never a therapeutic benefit for trial subjects expected. What should be expressed here is that the risk-benefit analysis has to be performed particularly carefully in FiM with high-risk drugs.            | <i>Participation in this type of studies is by definition not providing any potential therapeutic benefit to the subjects. In clinical trials with high-risk drugs particular emphasis has to be put on provision of an acceptable risk-benefit ratio and an optimal protection of the subjects during and after the study performance.</i>  |
| 1.<br>Introduction<br>23                     | In addition to the comments made above, please add:  | <i>Provisions have to be made that the clinical research unit is suitable and the clinical research staff adequately trained.</i>  |
| 4.1<br>66                                    | This paragraph defines “potential high-risk medicinal products when there are concerns that serious adverse reactions in first-in-man clinical trials may occur”.  | Comment: this should remain a temporary category until the first-in-man CTs have been completed with the medicinal product so labelled. A medicinal product for which the potential high-risk is not confirmed should lose this label at entering Phase II.  |
| 4.1,<br>68-69                                | This paragraph states that concerns may be “derived from (...) uncertainties about (1) the mode of action, and/or (2) the nature of the target, and/or (3) the relevance of animal models.”  | Comment: all three reference criteria for judging uncertainties are notoriously controversial subjects: modes of action of drugs are usually not fully clarified at the beginning of Phase I. The level of clarification of the mechanism of action (cellular, sub-cellular, molecular) never gives complete certainty about the mode of action of a medicinal product. Many physiological effects of medicinal products have been discovered before their mode of action could be even studied: e.g., aspirin was found to be a platelet aggregation inhibitor before it was discovered that aspirin blocks cyclooxygenase (COX). Also, medicinal products very frequently if not always multiple modes of actions, and one may be elucidated regarding the |

<sup>1</sup> Where available

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|                |   | <p>mode of action in the putative indication for the new medicinal product, whereas the other which is not even suspected may be associated with high risk. It would be wrong to (1) require a deep level of elucidation of a broad band of modes of actions of lead compounds before they go in first-in-man CTs as this would delay drug development potentially by months or rather years, and (2) require the lack of uncertainty regarding our knowledge of the mechanism(s) of actions, since elucidating mechanisms of action is a never-ending process. Mutatis mutandis, these observations apply to the nature of targets and animal models. Targets may be identified at sub-cellular level, e.g., at receptor level in the brain, and yet the precise role of the receptor may not yet be elucidated. By definition, animal models are only models, and therefore subject a priori to uncertainty. If there were no uncertainty left, the medicinal products would not have to be tested in man. Therefore, it is to be feared that an overcautious connection of risk with these uncertainties will lead to paralysis.</p> |
| 4.1<br>70-74   | <p>This paragraph states that for high-risk medicinal products conventional non-clinical programmes do not provide an acceptable safety estimate.</p> | <p>Since it is not possible to flag high-risk compounds, this requirement risks being interpreted practically as requiring more non-clinical research on all lead compounds. The words “acceptable safety estimate” introduce a medico-legal responsibility issue which is a moving target since it depends on who will judge the acceptability. This will lead scientists in the field of preclinical programmes and in Phase I to blame each other for being insufficiently conservative, hence the preclinical phase may become longer for all lead compounds because of increased responsibility to demonstrate safety beyond doubt and Phase I specialists may request more animal work before taking the responsibility of a first application in man.</p>  |
| 4.1<br>104-105 | <p>If animal models are of limited relevance.</p>   | <p>The Guideline should give a more precise reference, because if experts writing the guidelines cannot come up with workable solutions, there probably aren't. In practice, different parties will need to implement the Guideline in a way which allows consensus: ethics committees, sponsors, patient associations, the Phase I unit, all must know what “limited relevance means”, otherwise there will be chaos as the parties quarrel about the meaning of the limits of reasonableness.</p>   |
| 4.2<br>111     | <p>...insufficient knowledge for entirely novel types...</p>  | <p>Again, the Guideline lacks clear-cut standards for decision-making in an environment where many stakeholders have to make joint decisions. The word “insufficient” is used here without any reference point. There needs to</p>  |

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|                    |   | be a judge of what is sufficient and what is insufficient. If this is not done, the Guideline will spread among stakeholders a fear of taking responsibilities, which will lead to Phase I being transferred outside the EU territory of applicability of the Guideline. The word “entirely” novel is equally misleading, as no reference point is offered on which all parties can agree.  |
| 4.3.6<br>216-217   | ...in the most sensitive and relevant animal species  | The most sensitive animal species is either the most sensitive of a number of species tested, taking into consideration the actual species tested, or it is the most sensitive of all species which can be tested today. In other words the Guideline should recommend a relative approach or an absolute approach to rank species sensitivities. If this is not carefully worded, it will lead to animal overkill in the search for the most sensitive species in absolute terms.  |
| 4.4<br>259-260     | An independent safety monitoring board  | It is probably unrealistic to imagine that sponsors will pay for an IDSMB for each protocol. The CT Directive and its Guidance documents recommend an IDSMB in the context of high morbidity or high mortality studies, not Phase I studies.  |
| 4.4.1<br>265       | The Informed Consent process is of utmost relevance at this stage of drug development. This should be reflected in this guideline.<br>Suggested addition: | <i>The Informed Consent process should ensure a detailed communication of all potential risks and documented verification of the participants’ comprehensive understanding of the involved risks and the safe-guards, including the indemnity conditions in case of short- and long-term health damages.</i>  |
| 4.4.2.1<br>282-283 | Must not be simultaneously in another trial   | A volunteer died in 1985 at a Phase I unit in Dublin because of this issue. It is agreed that this is an absolute exclusion criterion. However, Phase I units depend on the honesty of volunteers in this regard. The Guideline should recommend measures which would create a really objective measure of participation in clinical trials, e.g., volunteers could be given a trial participation card, which must be filled out successively by all Phase I units for all volunteers. Entries could be anonymous regarding the Phase I units visited. A volunteer who “lost” his/her card would be denied access to any trial at any unit. However, this system relies on the honesty of Phase I units actually entering each study in every case. Violations could lead the Phase I unit losing its accreditation or qualification with its IEC. |

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| 4.4.2.4<br>294                        | Precautions between doses   | This sentence should be modified as follows:<br>For first-in-man trials with high-risk medicinal products, a sequential enrollment and dosage administration should be employed etc.  |
| 4.4.2.4<br>296                        | “..adequate period of observation”. This is too imprecise. The text should define the criteria, for example:                        | There must be <i>sufficient time between the</i> periods of observation of the first, second, and subsequent administrations <i>to observe and interpret reactions and adverse events</i> , depending on.....   |
| 3.1.5<br>Dose<br>escalation<br>scheme | Practical examples of suitable schemes should be given like starting with only one subject, pilot subjects in all dose levels, etc. |   |
| 4.4.3<br>356                          | More emphasis should be put on the assessment of suitability of the site.   | <i>The suitability of the site should be verified by the responsible ethics committee according to an agreed list of criteria. The implementation of an accreditation system for clinical research units performing FiM trials should be considered.</i>  |
| 4.4.3<br>357                          | Site of medical trial   | This line requires that medical staff should have an appropriate level of training and expertise, however, like in ICH GCP, it does not provide standards.  |
| 4.4.3<br>358                          | ...be conducted by medical staff with appropriate level of training and expertise.....  | <i>...be conducted by trained investigators who have acquired the necessary expertise in conducting early clinical drug trials (i.e. phase I-II) under well controlled circumstances. These studies should be conducted by medical staff with appropriate level of training and experience in early clinical drug development. Training in Good Clinical Practice, safety training and Basic Life Support should be considered mandatory for investigator and site personnel.</i> |

Please feel free to add more rows if needed.

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