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

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## EXECUTIVE SUMMARY

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

## 1. INTRODUCTION

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

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

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

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

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

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

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

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

*Non-clinical aspects:*

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

*Quality aspects*

[1] 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)

- EUDRALEX -Volume 4 - Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice. Annexe 13: Manufacture of Investigational Medicinal Products.
- Guideline on Virus Safety Evaluation of Biotechnological Investigational Medicinal Products - Draft- EMEA/CHMP/BWP/398498/2005-corr.
- Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials. CHMP/QWP/185401/2004

*Clinical aspects*

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

## 2. SCOPE

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

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

## 3. LEGAL BASIS

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

## 4. MAIN GUIDELINE TEXT

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

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

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

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

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

- Mode of action

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

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

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

- A mechanism that bypasses physiological control mechanisms, e.g. CD3 or CD28 (supra-) agonists.

sponsors should also discuss the novelty of the structure of the medicinal product, for example a new type of engineered structural format like bispecific antibodies or novel fusion proteins. Such products may be high-risk medicinal products even if the parent compounds are well established.

- Nature of the target

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

- the extent of the knowledge on the structure, tissue distribution, cell specificity, disease specificity, regulation, and biological function of the human target including "down-stream" effects.
- the relationship between the biology of the target, and the physiological or pharmacological effects, in both normal and pathological states.

- Relevance of animal models

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

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

## 4.2 Quality aspects

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

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

- Characterisation

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

- Determination of strength and potency

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

- Comparability with the material used in non-clinical studies

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

- Reliability of very small doses

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

## 4.3 Non-clinical requirements

### *4.3.1 Pharmacodynamics*

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

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

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

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

### *4.3.2 Pharmacokinetics*

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

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

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

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

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

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

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

The demonstration of relevance includes:

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

Where no relevant species exists, the use of relevant transgenic animals expressing the human receptor or the use of homologous proteins is strongly recommended.
The search for a relevant animal model should be documented and justified in detail.

### *4.3.4 Safety Pharmacology*

In addition to the core battery outlined in the CHMP/ICH guidelines S7A and S7B, for high risk medicinal products, additional studies to investigate effects in other organ systems should be carried out on a case by case basis. In particular, for medicinal products targeting the immune system, potential unintended effects should be investigated, *e.g.* using *in vitro* studies, including human material.

### *4.3.5 Toxicology*

The toxicology programme should be performed in appropriate animal species and include toxico-kinetics. The inclusion of relevant pharmacodynamic endpoints should be considered, where possible.
Toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged. When using a homologous or transgenic model approach, the information gained is optimised when the interaction of the product and the target receptor has similar physiological consequences to those expected in humans.
Animal models that are thought to be similar to the human disease may provide further insight in the pharmacological action, the pharmacokinetics, and dosing in patients. They may also be useful in the determination of safety (e.g., evaluation of undesirable promotion of disease progression). In certain cases, studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals. The scientific justification for the use of these animal models of disease to support safety should be provided.

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

In general, the calculation of the first dose in man is based on No Observed Adverse Effect Level (NOAEL) determined in non-clinical safety studies performed in the most sensitive and relevant animal species, adjusted with allometric factors or on the basis of pharmacokinetics. The relevant dose is then reduced/adjusted by appropriate safety factors according to the particular aspects of the molecule and the design of the clinical trials.
For high-risk medicinal products, an additional approach to dose calculation should be taken. The use of 'Minimal Anticipated Biological Effect Level' (MABEL) approach is recommended. The MABEL is the anticipated dose level leading to a minimal biological effect level in *humans*. Safety factors are usually applied for the calculation of the first dose in man from MABEL.

The calculation of MABEL should utilise all relevant *in vitro* and *in vivo* available information from pharmacodynamic/pharmacokinetic data such as:

i) receptor binding and receptor occupancy studies in vitro in target cells from human and the relevant animal(s) species and in vivo in the relevant animal species;

ii) concentration-response curves in vitro in target cells from human and the relevant animal(s) species and dose response in vivo in the relevant animal species.

iii) exposures at pharmacological doses in the relevant species.

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

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

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

## 4.4 Clinical requirements

### *4.4.1 General aspects*

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

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

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

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

### *4.4.2 Protocol design*

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

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

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

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

#### *4.4.2.2 Route and rate of administration*

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

#### *4.4.2.3 Choice of the first dose in human*

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

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

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

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

#### *4.4.2.5 Precautions to apply between cohorts*

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

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

#### *4.4.2.6 Dose escalation scheme*

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

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

#### *4.4.2.7 Stopping rules and decision making*

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

#### *4.4.2.8 Monitoring for adverse events/reactions*

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

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

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

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

Long term monitoring

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

### *4.4.3 Site of the clinical trial*

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

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

*Legal basis*


- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (*Official Journal L 121, 1/5/2001 p. 34 - 44*).

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use *(Official Journal L 311, 28/11/2001 p. 67 - 128)*.
  Consolidated Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use as amended by Directive 2002/98/EC, Directive 2004/24/EC and Directive 2004/27/EC. *(Official journal l – 311, 28/11/2004, p. 67 – 128)*

- Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial. October 2005 Revision 2


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

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