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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 7418 8613
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This guideline is intended to assist sponsors in the transition from non-clinical to early clinical development. It identifies factors influencing risk for new investigational medicinal products and considers quality aspects, non-clinical and clinical testing strategies and designs for first-in-human clinical trials. Strategies for mitigating and managing risk are given, including the calculation of the initial dose to be used in humans, the subsequent dose escalation, and the conduct of the clinical trial.

1. INTRODUCTION

The safety of subjects participating in first in human studies is the paramount consideration as they 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-human clinical trials must be science-based, and should be made and justified on a case-by-case basis.

Quality aspects should not, in themselves, be a source of risk for first-in-human trials. Nevertheless, special consideration should be given to certain factors which may add to the risk as described in this guideline.

The non-clinical testing and experimental approaches for first-in-human studies might identify potential factors influencing risk for investigational medicinal products. The ability of non-clinical studies to predict safety issues in humans may be limited 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 estimation 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 an investigational medicinal product information on safety 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 influencing risk to be considered in the non-clinical testing strategy and designs of first-in-human clinical trials for investigational medicinal products.

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

This guideline should be read in conjunction with the published EU guidelines (see also section references) and in particular the following:

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 Repolarisation (QT Interval Prolongation) by Human Pharmaceuticals (ICH S7B) CPMP/ICH/423/02
- Safety pharmacology studies for human pharmaceuticals (ICH S7A)- CPMP/ICH/539/00
- Toxicokinetics: the assessment of systemic exposure in toxicity studies (ICH S3A) - CPMP/ICH/384/95
- Position Paper on the non-clinical safety studies to support clinical trials with a single micro dose (CPMP/SWP/2599/02)

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- Volume 10 – Clinical trials. In particular: Chapter I: Application and Application Form and Chapter II: Monitoring and Pharmacovigilance.

2. SCOPE

This guideline applies to all new chemical and biological investigational medicinal products except gene and cell therapy medicinal products. It covers non-clinical issues for consideration prior to the first administration in humans and the design and conduct of trials in the initial phase of single and ascending doses during the clinical development.

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. (See references)

4. MAIN GUIDELINE TEXT

For many new investigational medicinal products, the non-clinical safety pharmacology and toxicology programme provides sufficient safety data for estimating risk prior to first administration in humans. However, for some novel medicinal products this non-clinical safety programme might not be sufficiently predictive of serious adverse reactions in man and the non-clinical testing and the design of the first-in-human study requires special consideration.

When planning a first-in-human clinical trial, sponsors and investigators should identify the factors of risk and apply risk mitigation strategies accordingly as laid down in this guideline. In addition to the principles expressed in this guideline, some special populations such as paediatrics may deserve specific considerations.

4.1 Factors of risk

Predicting the potential severe adverse reactions for the first-in-human use of an investigational medicinal product, involves the identification of the factors of risk. Concerns may be derived from particular knowledge or lack thereof regarding (1) the mode of action, (2) the nature of the target, and/or (3) the relevance of animal models.

The Sponsor should discuss the following criteria for all first-in-human trials in their clinical trial authorisation application. These criteria should be taken into account on a case-by-case basis.

- Mode of action

While a novel mechanism of action might not necessarily add to the risk per se, consideration should be given to the novelty and extent of knowledge of the supposed mode of action. This includes the nature and intensity (extent, amplification, duration, reversibility) of the effect of the medicinal product on the specific target and non-targets and subsequent mechanisms, if applicable. The type and steepness of the dose response as measured in experimental systems, which may be linear within the dose range of interest, or non-linear (e.g. plateau with a maximum effect, over-proportional increase, U-shaped, bell-shaped), is of importance.

For example, the following modes of action might require special attention:

- A mode of action that involves a target which is connected to multiple signalling pathways (target with pleiotropic effects), e.g. leading to various physiological effects, or targets that are ubiquitously expressed, as often seen in the immune system.
- A biological cascade or cytokine release including those leading to an amplification of an effect that might not be sufficiently controlled by a physiologic feedback mechanism (e.g., in the immune system or blood coagulation system). CD3 or CD28 (super-) agonists might serve as an example.

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

- Previous exposure of human to compounds that have related modes of action.

- Evidence from animal models (including transgenic, knock-in or knock-out animals) for the potential risk of serious, pharmacologically mediated toxicity
- Novelty of the molecular structure of the active substance(s), for example a new type of engineered structural format, such as those with enhanced receptor interaction as compared to the parent compound.

- Nature of the target

The target in human should be discussed in detail. Beyond 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, based on the available data:

- the extent of the available knowledge on the structure, tissue distribution (including expression in/on cells of the human immune system), cell specificity, disease specificity, regulation, level of expression, and biological function of the human target including "down-stream" effects, and how it might vary between individuals in different populations of healthy subjects and patients.
- If possible a description of polymorphisms of the target in relevant animal species and humans, and the impact of polymorphisms on the pharmacological effects of the medicinal product.

- Relevance of animal species and 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. (See also 4.3.1)

Where available animal species/models or surrogates are perceived to be of questionable relevance for thorough investigation of the pharmacological and toxicological effects of the medicinal product, this should be considered as adding to the risk.

4.2 Quality aspects

The requirements are the same for all investigational medicinal products regarding physico-chemical characterisation and, additionally biological characterisation of biological products (see references). Quality attributes should not, in themselves, be a source of risk for first-in-human trials. However, these quality attributes are to be considered in a risk assessment preceding a first-in-human trial.

Specific points to be considered are:

- Determination of strength and potency

To determine a safe starting dose, the methods used for determination of the strength and/or 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 their reliability, the doses used in non-clinical studies may be poorly defined and mislead the interpretation of what is a safe dose. Therefore it is important to have a representative defined reference material from early in the development programme to measure biological activity. For a biological medicinal product, the lack of a bioassay measuring the functional or biological activity should be justified.

- Qualification of the material used

The material used in non-clinical studies should be representative of the material to be used for first-in-human administration. It is important to have an adequate level of quality characterisation even at this early point of development. A characterisation of the product including its heterogeneity, degradation profile and process-related impurities should be performed. Particular attention should be given to impurities that could be pharmacologically active and/or toxic. Special consideration should be given to the suitability and qualification of methods to sufficiently characterise the active substance and drug product.
When moving from non-clinical studies to first-in-human administration, there should be sufficient assurance that product differences, should they occur, would not have an adverse impact on clinical

characteristics of the product, especially safety. Furthermore, 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 active substance that may not be detectable in characterisation studies but can affect 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 these data remain valid.

Further non-clinical studies may be needed with the product intended for use in the first-in-human trial in the following situations:

- Where there are differences in the product quality attributes of the non-clinical and clinical material and adverse clinical consequences may result from such differences.
- Where there are differences in the manufacturing process and the limitations of product characterisation, including biological assays, cannot assure that the material used in non-clinical studies is representative of the material to be used in clinical studies.

- Reliability of very small doses

Applicants should demonstrate that the intended formulation of the doses to be administered provides the intended dose. 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 as 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. Therefore, compatibility of the product with primary packaging materials and administration systems should be investigated, where relevant.

4.3 Non-clinical aspects

4.3.1 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 animal studies with highly species-specific medicinal products may:

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

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

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-human trials.

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

- Target expression, distribution and primary structure. However, a high degree of homology does not necessarily imply comparable effects;
- Pharmacodynamics
  - Binding and occupancy, functional consequences, including cell signalling if relevant.

- Data on the functionality of additional functional domains in animals, if applicable, e.g. Fc receptor system for monoclonal antibodies.

- Metabolism and other pharmacokinetic aspects
- Cross-reactivity studies using human and animal tissues (e.g. monoclonal antibodies).

The search for a relevant animal model should be documented and justified in detail.
Where no relevant species exists, the use of homologous proteins or the use of relevant transgenic animals expressing the human target may be the only choice. The data gained is more informative when the interaction of the product with the target receptor has similar physiological consequences to those expected in humans. The use of *in vitro* human cell systems could provide relevant additional information.
The relevance and limitations of all models used should be carefully considered and discussed fully in the supporting documentation**.**

4.3.2 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 models. The primary and secondary pharmacodynamics, should be conducted in *in vitro* animal and human systems and *in vivo* in the animal models. These studies should include target interactions preferably linked to functional response, e.g. receptor binding and occupancy, duration of effect and dose-response.

A dose/concentration-response curve of the pharmacological effect(s) should be established with sufficient titration steps in order to increase the likelihood to detect significant pharmacological effects with low doses and to identify active substances with U-shaped or bell-shaped dose-response curves. Such significant or even reverse effects have been reported with biological compounds. Since a low dose is to be administered to humans in the first-in-human 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.

4.3.3 Pharmacokinetics

Standard pharmacokinetic and toxicokinetic data should be available in all species used for safety studies before going into human (ICH S3, S6, M3).
Exposures at pharmacodynamic doses in the relevant animal models should be determined especially when pharmacodynamic effects are suspected to contribute to potential safety concerns.

4.3.4 Safety Pharmacology

Standard core battery data should be available before the first administration in humans (CHMP/ICH guidelines S7A, S7B, S6, M3).
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 relevant animal species and include toxico-kinetics.
When factors influencing risk are identified (see section 4.1), the inclusion of additional endpoints should be considered, on a case-by-case basis.

Toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged. The use of homologous products or transgenic model approach or of *in vitro* human cell systems could provide relevant additional information.
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 (e.g. presence of neutralising antibodies).

Animal models that are thought to be similar to the human disease may provide further insight in the pharmacological action, the pharmacokinetics, (e.g. disease-related expression of the target) as well as dosing in patients and safety (e.g., evaluation of undesirable promotion of disease progression). Therefore, 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 Estimation of the first dose in human

The estimation of the first dose in human is an important element to safeguard the safety of subjects participating in first-in-human studies. All available information has to be taken in consideration for the dose selection and this has to be made on a case-by-case basis. Different methods can be used.

In general, the 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 (see references "Other guidelines") or on the basis of pharmacokinetics gives the most important information. 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 investigational medicinal products for which factors influencing risk according to section 4.1 have been identified, an additional approach to dose calculation should be taken. Information about pharmacodynamics can give further guidance for dose selection. The '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. When using this approach, potential differences of sensitivity for the mode of action of the investigational medicinal product between humans and animals, need to be taken into consideration e.g. derived from *in-vitro* studies. A safety factor may be applied for the calculation of the first dose in human from MABEL as discussed below.

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

i) target binding and receptor occupancy studies *in vitro* in target cells from human and the relevant animal species;
ii) concentration-response curves *in vitro* in target cells from human and the relevant animal species and dose/exposure-response *in vivo* in the relevant animal species.
iii) exposures at pharmacological doses in the relevant animal species.

Wherever possible, 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, a safety factor may be applied in the calculation of the first dose in human from the MABEL. This should take into account criteria of risks such as the novelty of the active substance, its biological potency and its mode of action, the degree of species specificity, and the shape of the dose-response curve and the degree of uncertainty in the calculation of the MABEL. The safety factors used should be justified.

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

Other approaches may also be considered in specific situations, e.g. for studies with conventional cytotoxic IMPs in oncology patients. (See references "Other guidelines")

4.4 Clinical aspects

4.4.1 General aspects

The safety of participants in first-in-human clinical trials can be enhanced by identification and planned mitigation of factors associated with risk. Key aspects of the trial should be designed to mitigate those risk factors, including:

- study population;
- trial sites;
- first dose;
- route and rate of administration;

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

In general, the higher the potential risk associated with an investigational medicinal product (IMP) and its pharmacological target, the greater the precautionary measures that should be exercised in the design of the first-in-human study. The protocol should describe the strategy for managing risk including a specific plan to monitor for and manage likely adverse events or adverse reactions as well as the procedures and responsibilities for modifying or stopping the trial if necessary. The sponsor should arrange for peer review of the protocol and the associated risk factors and to assure that they have been properly considered and planned for.

It is recognised that placebo is often included as part of the design of Phase I studies. The study design including randomisation schemes should take this into account. Any decisions taken with respect to subsequent dosing at the same dose level and or to dose escalation, should take into account the number of subjects that might have received either placebo or the active medicinal product. There should always be rapid access to the treatment allocation codes when relevant.

For first-in-human trials where there is uncertainty about the risk it is recommended that a confirmatory pharmacodynamic measure is identified that can show the pharmacological effect and link with the preclinical experience.

4.4.2 Protocol design

4.4.2.1 Choice of subjects for first-in-human trials

Subjects are not generally expected to derive any therapeutic benefit from a first-in-human trial.
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, i.e. healthy subjects or patients, including special populations, 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 - it is important that those risks (and uncertainty about them) be quantified and justified;

(b) its molecular target,

(c) immediate and potential long term toxicity;

(d) the lack of a relevant animal model;

(e) the relative presence of the target in healthy subjects or in patients; e.g. cancer patients;

(f) the possible higher variability in patients;

(g) the ability of healthy volunteers to tolerate any potential side effects;

(h) the potential pharmacogenomic difference between the targeted patient group and healthy subjects;

(i) the patients' ability to benefit from other products or interventions; and

(j) the predicted therapeutic window of the IMP.

Where practicable concurrent medication in patients should be avoided as it, together with the disease state may give rise to greater variability in response and interactions, with the possibility for adverse reactions and/or difficulties in the interpretation of results.

Healthy subjects or patients should not be included in first-in-human clinical trials if they are in another clinical trial or have participated recently in another clinical trial unless justified. It is important to include clear exclusion criteria to prevent concomitant or immediate consecutive exposure to investigational medicinal products.

4.4.2.2 Route and rate of administration

The choice of route and rate of administration of the first dose in humans should be justified based on the non-clinical data. In the case of an intravenous administration, a slow infusion, may be more appropriate than a slow bolus. This would allow monitoring for an adverse reaction and, if clinically indicated, timely discontinuation of the infusion to mitigate a serious outcome.

4.4.2.3 Estimation of the first dose in human

The estimation 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

It will usually be appropriate to design the administration of the first dose so that a single subject receives a single dose of the active IMP. Further dose administration should be sequential within each cohort to mitigate the risk. Any non-sequential dose administration within each cohort should be justified. There must be an adequate period of observation between the administration of the medicinal product to the first, second and subsequent subjects in a cohort to observe and interpret reactions and adverse events. The duration of the interval of observation should be justified and will depend on the properties of the product and the data available, including non-clinical PK and PD. Experience and identified risk factors from trials with comparable medicinal products should also be considered.

The number of subjects per dose increment (the cohort size) depends on the variability of both pharmacokinetic and pharmacodynamic parameters and the trial objectives such as justifying progression to the next cohort. While larger cohorts are likely to provide more precise data, they may not be necessary to fulfil the objectives of the study.

4.4.2.5 Precautions to apply between cohorts

Where risk factors from section 4.1 are identified for the IMP there should be a precautionary approach to progressing to a subsequent cohort. Criteria should be pre-specified in the protocol that will be used to identify and mitigate the risk of progressing to a subsequent cohort. Administration in the next cohort should not occur before participants in the previous cohort have been treated and data/results from those participants are reviewed in accordance with the protocol. This may include comparison of PK, PD or PK/PD data from any previous cohorts with known non-clinical data and safety information to inform the decision. Any observed pharmacological responses should be compared to the responses that were anticipated. Unanticipated pharmacological responses may require a revised dose escalation. Time intervals between cohorts should be guided by non-clinical and clinical PK and PD data and if available, data from comparable medicinal products.

4.4.2.6 Dose escalation scheme

Dose increases should proceed with caution taking into account identified risk factors from non-clinical studies such as a steep dose-response curve, exposure-response and dose-toxicity curves.

The dose increment between two dose levels should be guided by the dose/toxicity or dose/effect relationship defined in non-clinical studies, depending on whichever is steeper where this information is available. 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. Since the initial doses may be very low, it is anticipated that early cohorts may not show any pharmacological effects. Where there is no response in a cohort the precautions for the next cohort should be the same as for the previous cohort.

4.4.2.7 Stopping rules and decision making

The protocol should define stopping rules for the cohort and trial. It should define processes and responsibilities for making decisions about dosing of subjects, dose escalation and stopping the cohort or trial. In the case of multicentre trials it is particularly important to define processes for immediate communications between sites.

4.4.2.8 Monitoring and communication of 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 investigational medicinal product, findings in the non-clinical toxicity studies and any anticipated responses should be used to identify likely adverse reactions. All clinical staff should be trained to identify those reactions and how to respond to those or any other adverse events or reactions. There should be constantly available rapid access to the treatment allocation codes when relevant.

In cases where there is a predictable risk of a certain type of 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, a clear plan of availability of supportive treatment emergency facilities and medical staff.

The length of the monitoring period and nature of monitoring within and if deemed appropriate outside the research site should be justified on the grounds of pharmacokinetics, pharmacodynamics and safety endpoints as part of the strategy to manage risks in the clinical trial. Special consideration should be given to potential long-term consequences on physiological systems and potential long-term safety problems.

Communication of serious adverse events 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)

4.4.3 Investigator site facilities and personnel

First-in-human trials should take place in appropriate clinical facilities and be conducted by trained investigators who have acquired the necessary expertise and experience in conducting early phase trials (i.e. phase I-II) and medical staff with appropriate level of training and previous experience of first-in-human studies. They should also understand the investigational medicinal product, its target and mechanism of action.

Units should have immediate access to equipment and staff for resuscitating and stabilising individuals in an acute emergency (such as cardiac emergencies, anaphylaxis, cytokine release syndrome, convulsions, hypotension), and ready availability of Intensive Care Unit facilities. Procedures should be established between the clinical research unit and its nearby Intensive Care Unit regarding the responsibilities and undertakings of each in the transfer and care of patients.

First-in-human trials should preferably be conducted as a single protocol at a single site. When different sites are involved this should be justified and an appropriate plan needs to be in place to assure the well-being of all trial participants and to assure an adequate information communication system. This information system should ensure that new safety findings are transmitted to all participating sites and that the integrity of the study design is not compromised.

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.

Guidance on quality aspects

- EUDRALEX -Volume 4 - Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice. In particular, Annex 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

Other guidelines

- Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. FDA/CDER, July 2005
- Pre-clinical evaluation of anti- cancer medicinal products (CPMP/SWP/997/96)
- Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95 Rev. 3)