



Federal Agency for Medicines and Health Products

Guidance to the conduct of exploratory trials in Belgium.

NOTICE:

This is a working document concerning the conduct of clinical exploratory trials in Belgium, while awaiting the development of guidelines at the European level. This document shall be discussed in different phases at the national level as well as at the level of EMA as appropriate. Some of the contents already reflect views that were recently discussed at ICH. This document should not yet be considered as a final point of view of the Federal Agency for Medicines and Health products in Belgium (FAMHP).

Introduction.

The number of new medicines that progress throughout the full development to a final market authorisation is low. The development of new medicines involves a lot of resources. Thus, the failure of many new medicines to progress to final marketing authorisation results in resources being diverted from the development of promising new medicines and therefore these may become available to the patients later than could have been the case or some promising new medicines may not at all become available to patients. If specific critical questions could be answered with data obtained in humans before starting a formal development project, a better documented decision to proceed or not with a full development program could be made. A lot of resources could thus be devoted to a more rational development of the most promising new products. Therefore there is a need for exploratory trials in humans. By definition an exploratory trial will result in providing an answer to a specific question with a limited human exposure in terms of dose, time and number of participants to the study. Exploratory studies will have no therapeutic or diagnostic intent.

- To confirm the presence of a biological pathway/mechanism activity in humans
- To establish if a new medicine possesses an acceptable pharmacokinetic profile at pharmacological doses
- To establish the validity of non-clinical disease models to human disease
- Characterize biomarkers of human disease and a pharmacodynamic response to a new medicinal product in minimally diseased patients

- Validate clinical models in healthy volunteers
- Correlate binding with effect and refine PK/PD modeling and simulation
- Compare human ADME or pharmacodynamic parameters across candidates
- Investigate potential for drug-drug interactions
- Evaluate binding affinity or metabolites produced in humans
- Establish the novelty of a potential therapeutic target in comparison to other established therapies.
- Identify differences between healthy volunteers and patients related to pharmacodynamic response sensitivity

The safety of the participants to such studies is paramount but without jeopardising their safety, the pre-clinical testing and the quality requirements for exploratory clinical trials may be less demanding than that normally expected for a phase 1 trial, because exposure will be limited and there will be no intent to reach doses that may cause toxicity. Because of the differences with phase 1 trials, guidance should be given about the chemical and pharmaceutical quality requirements and the pre-clinical data that are needed to support exploratory trials. So far in the EU there is only a concept paper from EMEA available on non-clinical studies to support exploratory clinical trials (EMEA/CHMP/SWP/91850/2006), and a position paper by EMEA concerning the use of a microdosing (EMEA/CHMP/SWP/2599/02/Rev1). In the US there is a Guidance for Industry, Investigators and Reviewers on Exploratory IND Studies (FDA, January 2006). While the EMEA position paper on microdosing is applicable in principle to Clinical Trial Applications that are submitted to the Competent Authority in Belgium, it does not cover exploratory clinical trial applications other than those making use of microdosing. It is very likely that other exploratory clinical trials with pharmacologically active doses at the low end of the dose response curve and without approaching a maximal tolerated dose will be needed. Based on the FDA paper and while awaiting a European guideline, a number of recommendations could be done in order to offer a temporary framework for preparing and evaluating exploratory clinical trial applications that are outside the scope of the microdosing approach and to be conducted in Belgium. According to the Belgian law of May 7th 2004 the evaluation of clinical trials is the responsibility of both the Competent Authority and the Ethics Committee when a new medicine without marketing authorisation will be used or when the use of a product with marketing authorisation outside the scope of its authorised use is envisaged. The present document is only referring to exploratory clinical trials to be conducted in Belgium that need to be submitted to both the Competent Authority and the Ethics Committee.



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Pre-submission meeting

Less pre-clinical testing will be required to support exploratory clinical trials in comparison with classical phase 1 trials. Thus relatively limited data will be available and it should be ascertained that these will be sufficient to support a trial. Also some flexibility with regard to the pre-clinical testing program according to the question to be answered in an exploratory clinical trial may be needed. Targets may involve mechanisms that were never explored in humans, potentially resulting in a high risk because the response in humans may be unexpected. Because exploratory trials may involve a certain degree of uncertainty and some flexibility may be required, it is strongly recommended to have a pre-submission procedure. After having paid the requested fee, the applicant should therefore write a letter indicating the intention to conduct an exploratory clinical trial to the department of Research & Development at the Federal Agency for Medicines and Health Products, Victor Hortaplein 40, 1060 Brussels. This letter should mention an EudraCT number and give a brief outline of the goal of the intended study, an overview of the planned pre-clinical experiments, the type of substance involved and the CPD data (Chemical and Pharmaceutical Data) and the pre-clinical data that will be available at the time of submission. The letter should also indicate the questions that the applicant may have about regulatory aspects concerning the planned trial. The information presented should allow the FAMHP to decide whether a formal meeting at its offices, a teleconference or a written procedure may be required to discuss the planned trial. This procedure will allow to determine on beforehand whether proposed testing programs will be sufficient to support an exploratory clinical trial and also to consult external experts in a given field if new targets will be addressed by the exploratory program. This may also be the most efficient way to pre-empt major concerns that may arise after evaluating the presented data. Preferentially, the (principal) investigator should also be present if a teleconference or a formal meeting is required. Since the Ethics Committee will also be involved in the evaluation of the clinical trial application, a representative of the Ethics Committee will also take part in the pre-submission procedure.

A formal meeting may not always be needed in many cases involving comparison of different candidates acting on a known target. A rational use of pre-submission contacts as stated above will be of value to maintain the quality of the review and may be helpful to maintain a short time span of 15 calendar days for adequate review of exploratory clinical trial applications once they are submitted. The time required for the pre-submission procedure can depend upon the complexity, the novelty of the target, the completeness of the dossier but will be kept as short as feasible.

Procedure

An exploratory trial should be submitted as a phase 1 trial with first administration to humans until exploratory early phase trials are formally recognised in the EU. In the EudraCT form the applicant should tick box E 7.1 and E 7.1.1 as well as E 7.1.3. There the applicant should clearly indicate that an early phase exploratory trial application is submitted. Different products can be included in one clinical research protocol that will lead to answering a specific question, and the CTA can be filed under one EudraCT number. The validation of the dossier will address the exploratory nature of the clinical trial application and therefore it must be clearly indicated why the trial will be exploratory in a covering letter. The aim of the trial or trial program must also be explained in that letter. If there is experience in humans with similar substances (based on chemical or pharmacological similarity, nature of the biotechnological product etc.), this should be described in a separate section of the clinical trial application. In Belgium 15 calendar days are allowed for review of a clinical trial application in phase 1 as described by the law of May 7th 2004. If the pre-submission procedure has been followed, the timelines for the evaluation of a phase 1 trial should normally be met, also for an exploratory trial. Given the specific nature of an exploratory trial, this cannot be guaranteed without pre-submission procedure. When a potentially high-risk product is involved, the time that is required for the clinical trial application to be reviewed before the start of the trial may need to be increased in order to consult with external experts in the particular field of research. The 15 day review period is currently calculated for one compound; additional time should be needed for additional compounds in a protocol. Since there is not yet a legal basis, provisional timelines are put forward. The 15 days that are prescribed by law for a phase 1 clinical trial review, plus an additional 3 days per additional substance will be the basis for calculation of review timelines. Once the actual data are submitted in an IMPD, the FAMHP may still exceptionally propose a meeting at its offices or a teleconference to solve any major concerns that did arise in the most efficient way.



Types of exploratory trials

Obviously the simplest form of an exploratory trial would involve only one single dose exposure for each study participant. However, it could be necessary to perform single dose escalation trials in order to study pharmacokinetics at therapeutic doses or to perform a pharmacodynamic assessment. The latter may aim at the study of target engagement in a particular effect and involve experimental medicine studies. It could also be that a single dose escalating trial would be performed to study efficacy of the product, which would mean that the difference with a classical phase 1 trial might become small. Yet the maximal tolerated dose should not be reached in the exploratory trial and the trial protocol should clearly indicate what the maximally required pharmacological effect would be to answer the questions that are decisive on the progress to formal development. Dosing should not be in excess of that needed to answer the questions that are the subject of the trial. In the case of dose escalation, more pre-clinical data may be needed to support the trial, at least in terms of the highest dose tested. Multiple dose studies may be necessary if a target needs time to be induced or in order to study the hyperacute effects of a product versus more sustained effects. If there is induction of a target or process, pre-clinical studies may need to address the reversibility of that effect. Repeat single dose studies may be required for cross-over designs (comparison of compounds), PET studies, the testing of formulations or to study drug-drug interactions.

Differences between exploratory trials and classical phase 1 studies

- A. Exploratory trials are designed to provide an answer to a specific question that needs to be well defined and that will allow selection or deselection of a compound or mechanism for further development. Exploratory trials will not be aiming at establishing an MTD, will not have tolerability as primary research objective and will not study long term efficacy. The limitation in the clinical dose means that there should either be no pharmacological effect at all or that the pharmacological effect should be limited to the extent needed to select a substance for further development or to validate a concept or approach as potentially promising to treat certain patients. The duration of the exposure of humans to a new medicinal product should not exceed the time required to observe the anticipated effect. The number of study participants should also be limited to the minimum required to answer the decisive question about further development.



Exploratory trials may allow the use of multiple compounds and short term readout and allow testing of PK/PD, changes of a biomarker or occupancy of the target. Limited compound synthesis and disposal would be needed to be able to conduct an exploratory trial, both for the clinical trial itself as for the pre-clinical program. Single batch qualification would be preferable. There would be limited animal usage because of the limited testing requirements.

- B. Phase 1 trials would establish a full tolerability profile, involve early safety determination, will be dealing with a single compound and a larger subject participation would be needed. Phase 1 trials would be staging for long-term studies and there should be a commitment to longer duration testing. The resource commitment is much higher in terms of number of animals and amounts of product required. Phase 1 trials will require synthesis and in case of failure disposal of several kilograms of substance. A multi batch qualification will be needed. At present there is a high failure rate, but if exploratory trials will be effective the failure rate in phase 1 trials should drop.

Chemical and Pharmaceutical Data (CPD)

1 Chemical entities considered as investigational medicinal products

The quality evaluation will be done according to the guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004 final), note for guidance on good manufacturing practice for active pharmaceutical ingredients (CPMP/ICH/4106/00), note for guidance on minimising the risk of transmitting animal spongiform encephalopathy via human and veterinary medicinal products (EMEA/401/01) and Eudralex volume 4, annex 13 on the manufacture of investigational medicinal products.

The following information concerning the drug substance should be available:

- Description of the drug substance, including physical and chemical characteristics
- Name and address of the manufacturer
- General method of drug substance preparation (if control of any manufacturing step or intermediate has been identified as critical to the quality of the Drug Substance, tests and acceptance criteria for control should be briefly summarised)
- Acceptance limits (and a brief justification) and analytical methods used to assure the identity and purity of the drug substance. (information on the validation of the analytical methods would not be required at this stage unless multiple batches would be produced).
- Information to support stability of the drug product for the proposed clinical studies

Two different scenarios may exist with regard to the analytical characterisation of the drug substance:

A. The batch of active pharmaceutical ingredient for pre-clinical and clinical use is different.

In this case the similarity or representative nature of batches should be demonstrated by analytical controls (identity, purity, biologic potency, residual solvents and heavy metals. Structural aspects should be defined in some cases, e.g.: optical rotation (for chiral compounds), reducing/non-reducing electrophoresis (for proteins). In essence, a comparison of the new batch(es) with those used in toxicology testing should ensure that foreseeable risks have been appropriately covered by the pre-clinical program.

B. The batch of active pharmaceutical ingredient for pre-clinical and clinical use is the same.

In this case there is no need to prove similarity, the impurity profile is not needed unless purity is below 95%, optical rotation needs not to be reported. It should be noted that for future reference and comparison it may be advisable to have some data available. In case there are obvious problems during the toxicological qualification the impurity profile and the optical rotation may be determined as needed.

The following information on the drug product should be available:

- List of components used in the manufacture of the investigational product
- Quantitative composition of the drug product
- Name and address of the manufacturer
- Brief general description of the method of manufacture and packaging (include sterilization process for sterile products).
- Ex-temporaneously prepared oral solutions/suspensions are most often prepared by a hospital pharmacist at the investigator site as multi-dose preparations without or with minimal specifications "at release". When such solutions are used, the IMPD should provide general information on the reconstitution. This should include the choice of the diluent. It should also address compatibility issues and stability if not used immediately. These aspects are considered to be under the direct control of the sponsor. In-use stability and dose accuracy should be ensured. The procedure and conditions in which the finished drug product is being extemporaneously prepared, stored until patient administration and dispensed should therefore be clearly defined in the protocol and in a document available to the hospital pharmacist. The application of the procedure for extemporaneous preparation in accordance with the guidance that is provided is under the control of the investigator and the hospital pharmacist at the investigator site.
- Acceptance limits (and brief justification) and analytical methods used to assure the identity, strength, and purity of the drug product. (information on the validation of the analytical methods would not be required at this stage unless multiple batches would be produced).
- Information to support stability of the drug product during the proposed clinical studies
- Copies of IMP labels.
- In case of parenteral administration sterility, amount of endotoxin and of particulate matter should be tested and reported.
- When the drug product is intended for inhalation, specific tests like particle size distribution measurement should be available.



- For testing requirements of any formulation, the PhEur or EU member state pharmacopea, the US pharmacopea or the Japanese pharmacopea should be consulted.
- Excipients should be listed in the PhEur or a EU member state pharmacopea, the US pharmacopea or the Japanese pharmacopea for the same route of administration and amount or they should appear on the GRAS (generally recognised as safe) list issued by FDA (<http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>). The use of novel excipients should be justified and the excipient should be fully characterised for the chemical, manufacturing and controls aspects as indicated by the EMEA note for guidance on IMP's and any novel excipients should be adequately qualified through appropriate animal studies.

As a general rule, GMP procedures apply to the manufacturing of IMP's intended for clinical trials including exploratory trials (Eudralex volume 4, annex 13). Controls should be consistent with the stage of development of the drug product (ICH note for guidance Q7). For exploratory clinical trials it would for instance be acceptable that development labs and pilot plants would produce the relatively small quantities of product needed. It may be acceptable that facilities and equipment are appropriate, raw materials and intermediates are well described, the final active pharmaceutical ingredient and the drug product are well characterised, the documentation would be sufficient to trace the whole production process and that the personnel responsible for the production is sufficiently skilled and well trained to have an acceptable IMP for an exploratory trial.

Any deviation from normally applicable guidelines governing quality aspects must be discussed during the pre-submission procedure and must be agreed upon by the FAMHP.

2 Biotechnological products

In as far as applicable, the principles outlined above for chemical entities should be practiced. Generally speaking the guidelines CPMP/BWP/328/99, CHMP/BWP/398498/2005, CHMP/BWP/2458/03, Eudralex 3AB1a, Eudralex 3AB2a, Eudralex 3AB3a, Eudralex 3AB4a, Eudralex 3AB5a, Eudralex 3AB6a and Eudralex 3AB7a are applicable with regard to all quality criteria for exploratory clinical trials using biotechnology products. The pre-submission discussion between the FAMHP and the applicant would offer the occasion to discuss any anticipated deviation from the normally applicable quality rules.

3 Investigational tools

It is conceivable that certain exploratory trials may involve products that are not intended to become medicinal products and that may be present under physiological or patho-physiological conditions in humans. These may be used to investigate the validity of a target in human disease, to evoke a response that could be validated as a biomarker or that could be used to investigate the effect of the exploratory medicine(s). In such cases, the investigational tool can be considered as a non-investigational medicinal product (NIMP) as defined in Eudralex volume 10, chapter V on clinical trials. For NIMP's without a marketing authorisation, in principle, the same criteria as for chemical or biotechnological entities will apply as described above. During the pre-submission contacts, it may be discussed whether or not it could be justified that particular exceptions to the general rules would be made.

4 Radiopharmaceuticals

In order to start a clinical study with radiopharmaceuticals in Belgium, approval should be obtained not only from the Belgian health authorities and the involved ethics committees but also from the Federal Agency for Nuclear Control (FANC). Prior to submission of the clinical trial application to the Belgian health authorities and the involved ethics committees, the applicant of the clinical study should ensure that all activities related to the use of the radiopharmaceutical in the context of the clinical study (eg. transport, storage, manufacture, patient administration of the finished product, etc.) are fully covered by the appropriate licenses issued by the FANC (i.e. for every investigator site involved in Belgium). More information on the FANC can be found on the following website: <http://www.fanc.fgov.be/> With regard to radiopharmaceuticals, the guidelines 3AQ20a and 3AQ21a apply in addition to the CHMP/QWP/185401/2004 guideline of the EMEA. Furthermore, reference is made to the draft Guidance on PET drug products - cGMP (FDA, September 2005). During the pre-submission contacts, it may be discussed whether or not it could be justified that small exceptions to the guidelines above would be made.



Pre-clinical testing: pharmacology, safety pharmacology and toxicology information

1 Chemical entities considered as investigational medicinal products

In principle there are 2 major scenarios that can be distinguished: the product to be investigated shall be used at a dose that does not exert a pharmacological effect or the product to be investigated shall be used at a dose that induces a pharmacological effect. Below two different pre-clinical testing approaches are proposed. It is conceivable that the need for pre-submission contacts can be reduced to a minimum in the future, once experience has been gained in using these approaches in a more routinely fashion. In both cases it would be expected that all available background information on the substance obtained during the screening with regard to primary activity, vital organ function and other safety parameters including the ligand-interaction profile in vitro will be submitted with the clinical trial application file. Whereas screening data are not expected to be obtained in accordance with GLP procedures, all safety related studies that are proposed below should be performed according to GLP procedures.

A. Microdosing

Exploratory studies that involve the use of pharmacologically inactive doses in a clinical trial should follow in first instance the microdosing approach as proposed by EMEA (EMEA/CPMP/SWP/2599/02/Rev1). Such studies would aim at the characterisation of the substance's pharmacokinetic or distribution properties, or receptor selectivity profile using positron emission tomography, accelerator mass spectrometry or other suitable very sensitive analytical techniques. A microdosing is defined by both EMEA and FDA as a dose less than 1/100th of the dose of the test substance that is calculated to yield a pharmacological effect in humans, based on animal data. The EMEA paper specifies that data obtained in vitro and in vivo may be used to predict the potency. The selection of the dose that is expected to cause no pharmacological effect in humans should be justified, but in the absence of contraindications the NOEL established during pharmacological testing in animals could serve as the reference if appropriate scaling is applied. The animal species that is used to determine the pharmacodynamical activity should be justified. Both EMEA and FDA specify that the maximum dose should be below 100 µg. Whereas this is generally acceptable, this may still be a fairly high dose for a very potent substance and a low dose for a less potent substance. This means that the potency criterion should be taken into account.

Since the molecular weight will usually not be extremely high for chemicals, it may play no major role for most chemicals with regard to the 100 µg limit, but it should be taken into account when relatively large molecules are considered. This would for instance be important when the new candidate medicine is a protein. If the intention is to protect the study participant from off-target toxicity or toxicity related to impurities the 100 µg limit may be sufficient in most cases, but also here an upper safety limit based on 1/100th of the NOAEL may be a more realistic measure to allow the safe conduct of a trial than the fixed amount of 100 µg. The total dose of 100 µg can be given to humans in one dose or divided over a maximum of 5 administrations. In conclusion for the microdosing approach, the total dose should thus not exceed 100 µg and each dose should not exceed 1/100th the NOAEL after proper scaling as determined in a toxicology study or 1/100th the pharmacodynamically active dose. If the conditions to use the microdosing approach are satisfied, an extended single-dose toxicity study in a rodent species, could replace the ICH M3 recommendations for safety pharmacology, single dose toxicity studies and repeated dose toxicity studies that would be required for other clinical trials. If a compound with low toxicity will be used, a limit dose of 10 mg/kg in rats is acceptable. This would allow to reach a safety margin of approximately 1000 or more at the limit dose, taking into account the proper scaling. The extended single-dose toxicity study would include an early sacrifice group at 2 days and a group that will be sacrificed after 14 days. Reversibility of the potential effects should only be studied in the high dose group. It is proposed that the two-day group would include more animals than the 14-day group and a ratio of 2:1 may be considered. The EMEA guideline proposes two routes of exposure for the extended single dose study: intravenous administration and the route that is going to be clinically used. If sufficient exposure is guaranteed and rational extrapolation to the human dose is possible, one route of exposure is also acceptable. The route of exposure and its justification may be discussed at the time of pre-submission. The EMEA guideline proposes genotoxicity testing, that may be abridged if sufficient data are available with similar compounds. If there are no structural alerts, genotoxicity testing may however not be necessary for microdosing purposes. If genotoxicity studies have been performed with the substance, these should be submitted. The appropriate receptor or other target screening profiles for the compound should also be made available. The microdosing approach as proposed above would not be applicable when the total amount of substance would be higher than 100 µg, even if 1/100th of the NOAEL or 1/100th of the pharmacodynamically active dose after proper scaling would not be exceeded. In that case an alternative testing can be proposed if the additional conditions are fulfilled that each of maximally 5 allowed doses would not exceed 100 µg and a wash-out between doses of 6 compound half-lives is allowed.



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An acceptable pre-clinical study package should then consist of a 7-day toxicology study that includes toxicokinetic and histopathological assessment in one rodent species by i.v. route or by the intended route of clinical administration, an appropriate characterisation of pharmacology in a relevant species that should be justified, an AMES assay or appropriate alternative if necessary and finally an appropriate receptor or other target screening profile.

B. Pharmacologically active dose

B1. Repeat dose toxicology studies of 14 days and confirmation of NOAEL in a non-rodent species

If it is necessary to study pharmacological effects of candidate products an exploratory clinical trial application can to a large extent be based on the second example about exploratory clinical trials to study pharmacologically relevant doses as described in the FDA guidance document. Repeat dose clinical trials lasting up to 14 days can be supported by a 2 week repeat dose toxicology study by the clinically used route of exposure with toxicokinetic evaluations to support that sufficient exposure has been attained. It could be justifiable to use other dosing schedules than once daily depending on the proposed clinical dosing schedule and the pharmacokinetic properties of the compound. The rat is the usually preferred species, but other animal species that are regularly used in toxicology testing may be selected. Justification about the species that is selected should always be given (see further). The aim of this 2 week repeat dose study is to establish a safe starting dose and a maximum dose for the clinical trial. The study should be conducted according to the same principles that are usually required from a toxicological study supporting a classical drug development trial, including adherence to GLP. A second non-rodent species that may often be the dog should be used to confirm that the first species is appropriately sensitive. The second species could be also another species that is often used in toxicology testing and its choice should always be justified. If there are no gender differences in the first species and if only one sex will be studied in the clinical trial, the study in the second species may be limited to only one sex. The number of animals in such a study can be limited: statistically significant differences are not required, but the study must allow to rule out any difference in sensitivity with the first species. The confirmatory study in a second species may be aiming at repeatedly administering a dose that is approximately the NOAEL in the first species calculated on the basis of body surface area. The number of administrations of the product should be at least the number of intended administrations in the clinical trial. Alternatively, an escalating dose study in the second species may be envisaged where in the end at least as many repeated doses as intended in the clinical trial will be administered to the animals at the NOAEL in the first species.



Should the second species be more sensitive than the first species, either the exploratory approach will be considered not possible or the applicant may wish to repeat a 2 week GLP toxicology study in the second species. The exposure in humans should not be higher than the AUC at NOAEL in the non-rodent species or than $\frac{1}{2}$ the AUC at the NOAEL in the rodent species.

Safety pharmacology studies will be required for this approach. The central nervous and respiratory systems will usually be evaluated in a rodent species and if the species selected for the first toxicology study was the rat or the mouse, this evaluation can be performed as part of the toxicology study. Cardiovascular safety will be evaluated in a non-rodent species, usually the dog and perhaps in some cases a non-human primate. This investigation can be part of the confirmatory toxicology study in the second species.

Genetic toxicology should be studied and should include a bacterial mutation assay with and without metabolic activation in five tester strains, and an in vitro test for chromosomal damage. An in vivo micronucleus test can be performed instead of the test for chromosomal damage in vitro. In that case a micronucleus assay in conjunction with the repeated dose toxicity study in rodents would be acceptable if the high dose is the maximally tolerated dose in the species used. All available data generated during the screening and all PK/PD information from animal models should be included in the clinical trial application file when this approach is used.

B2. Repeat dose studies in a rodent and a non-rodent with restriction of the maximal exposure in animals to 10 fold the expected human exposure.

Alternatively to the toxicological testing for 2 weeks in one species, usually a rodent, and confirming the NOAEL in a second species usually the dog, one could also investigate the toxicity of a product in two species (rodent and non-rodent), giving equal weight to both species but restricting the maximum dose used to one that achieves a multiple of the clinical exposure but not necessarily the MTD. With this approach toxicology studies of 14 days duration in rodents and non-rodents should be conducted, using 10 animals/sex/group for the rodent study and 3 animals/sex/group for non-rodents. The studies should use the intended clinical route of administration. The studies should include appropriate toxicokinetic assessments (AUC and C_{max}) and all of the endpoints typically incorporated into a conventional repeat dose toxicology study, and be conducted according to GLP standards. If such toxicity studies are conducted there are two possible outcomes; the study will either demonstrate target organ toxicity or it will not.

If the study adequately characterises the toxicity of the molecule, the exploratory clinical study could proceed as planned and, if results from this were favourable, there would be no barrier to progressing to higher clinical exposures or repeat dose studies of up to 14 days duration, subject to a standard safety/risk assessment taking account of the nature, severity, monitorability of the preclinical findings. In the case where no toxicity is observed in animals with a substance, human dosing based on exposure (AUC) should be capped at 1/10th of the maximum exposure obtained in animals at which no toxicity was observed and the duration of dosing in man should be limited to 14 days, i.e. the duration of the toxicology studies. Dose escalation in the clinical trial should then proceed from a low starting dose until the desired exposure in humans is reached based on measurements of AUC and C_{max} in humans. The 10-fold safety margin is supported by a survey conducted by EFPIA involving 60 first trial in human packages, the data from which has been made available to the Belgium Regulatory Authorities. Before exceeding these exposure and duration limits or progressing to conventional Phase I studies, further pre-clinical work using higher doses/exposures or longer durations of treatment would be required to identify the most sensitive target organs and more fully characterise the toxicity of the molecule. This approach can also be extended to Safety Pharmacology studies, which if conducted as stand-alone studies, would use the same upper dose limits as the repeat dose toxicology studies. Alternatively, where feasible the Safety Pharmacology endpoints could be incorporated into the appropriate repeat dose toxicology study. Genetic toxicology studies should conform to ICH S2 requirements.

All available data generated during the screening and all PK/PD information from animal models should be included in the clinical trial application file when this approach is used.

2 Biotechnological products

In principle the same guidance applies as that described for exploratory clinical trials with chemicals. It should however be recognised that species specific mechanisms of action will be much more likely with biotechnological products than with chemicals. Therefore the selection of the species to study primary action and safety aspects needs careful consideration. It could well be that only one species is acceptable and it may even be that in some cases no species at all is suited. Use of animal homologues to human products and targets or genetically engineered animals may be required in the event that no animal species is comparable to humans. In vitro data obtained on human cell lines may also play a more prominent role. It is very likely that the half-life of the product will be much longer than with chemical products. Therefore repeated daily administration to animals or humans may not be acceptable and a dosing schedule adapted to the product may be required.



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If the medicinal product to be investigated is a biotechnology-derived product and in particular if it is an agonist targeting the immune system, it should be specially considered whether or not species specific or potentially massive reactions are to be expected, taking into account the proposed mechanism of action, literature data on the target and in vitro data obtained with the product.

3 Investigational tools

If products will be used in an exploratory trial as investigational tools, in principle the same amount of testing will be required as if it were a candidate new drug substance. If this product is already well known and if sufficiently confirmed literature data are available this may however be superfluous. Nevertheless, since data may not have been obtained under GLP conditions and the applicant nor the competent authority have any control over the literature data and how they were gathered, it would be advisable to have at least some confirmatory data available that were obtained under GLP conditions, certainly when the product is still relatively new. It should also be considered whether it would be more important to construct a dose response curve for acute effects and observe the animals during two weeks to detect delayed effects that may occur after a single exposure, rather than conducting a repeat dose toxicity study.

4 Radiopharmaceuticals

The evaluation of radiopharmaceuticals should address both general parameters of the medicinal product and radiation dosimetry aspects. Guidelines with regard to the dosimetry and all necessary precautions related to the use of radiopharmaceuticals should always be observed, also in an exploratory clinical trial. It should also be justified why no alternatives to radiopharmaceuticals can be used. It is not the intention of this guidance document to consider the use of radiopharmaceuticals that will be administered as radiotherapy. Knowledge of the toxicology of the ligand per se is the first aim of pre-clinical safety testing and therefore safety studies may be conducted with unlabelled compound.



Choice of animal species

The selection of the animal species to be used in the experiments described above should be justified. This is particularly important if only one species can be used.

For the study of “off-target” toxicity, the rat and the dog would be convenient as they would allow the use of established routine procedures and this would have the advantage of a large database of experimental data for comparison being available. If the target of the candidate drug substance(s) would be known and already studied in humans, and therefore “on target” untoward effects would be known, the rat and the dog would be the normal choice to cover any “off-target” adverse effects. Obviously, *in vitro* metabolism data may confirm this choice or may lead to the proposal of an alternative, based on the comparability of the metabolism of the substance in humans and animals. When the target is new and not previously studied in humans, it should be assured that the target is present and operational in at least one of the animal test species that are used for safety testing. Otherwise, potential “on target” adverse effects would not be detected in pre-clinical tests. Although this would not be very likely the case for a medicinal product of chemical origin, it can be anticipated more often if the product is of biotechnological origin. In these cases “off target” toxicity may still be determined when using routinely used animal species for safety testing, but alternative models like genetically engineered animals and animal homologues may be envisaged to study potential “on-target” effects. It should be ascertained that the tissue expression, second messenger mechanisms etc. are comparable in the animal and the human in case genetically engineered animals would be a realistic testing possibility. In the case that animal homologues of a human target would be used, consideration should not only be given to the similarity of molecular targets (second messengers, nature of the effect, tissue distribution) but when the substance is produced by biotechnological means also to the production process and possibly resulting impurity profiles.

By using human cell lines and animal cell lines or organs *in vitro* that contain the target, it should preferably be known whether the potency of the test compound(s) would be similar, higher or lower in humans and the species used for safety testing. This may allow to calculate starting and maximal doses for the clinical trial more precisely by adjusting for species differences and may allow the use of a more realistic safety factor than the arbitrarily chosen ones to take species differences into account.

Often it is well known to what extent an homology exists between a human and animal target in terms of for instance amino acid composition. The question remains to what extent differences between targets are acceptable to predict human reactions based on observations in animals.



Indeed, even relatively small differences of the target may result in major potency differences. The use of in vitro data to compare animals and humans may make the question obsolete how much homology between both is sufficient to reliably extrapolate from the one to the other or at least represent valuable additional information. The potency of a test compound, its maximal effect and the type of response as well as the second messengers involved in the response could all be of value to enhance the predictability of the experimental data. Which in vitro data are required should be determined on a case by case basis and it should be justified why the data used are relevant to sufficiently predict responses in humans.

Starting dose

There are two well accepted ways of estimating a safe starting dose that could be applicable to exploratory clinical trials. One is the estimation of a Minimal Anticipated Biological Effect Level (MABEL) and the other is the use of 1/50th of the NOAEL in the most sensitive species. A systematic comparison of both by the Competent Authority might be of value to define the best procedure to establish a starting dose in the future.

If the mechanism of action of the medicinal product(s) to be used in the trial is well known, the pharmacological activity and the target-related or structure-related adverse effects are well known. Hence “off-target” toxicity may be of more concern than “on-target” toxicity. The 1/50th of the NOAEL after scaling (mg/m²) may be most realistic of the two approaches for calculating the starting dose in this case.

Alternatively, the starting dose in a clinical trial can be defined based on the pharmacological activity and then a projected clinical MABEL will be defined. There are various parameters that can be used for estimating MABEL. One is to model the occupancy of the target with different doses, another is to test effects on human tissues ex-vivo and a third possibility is to use data from a carefully qualified animal model. Dose- or concentration- response data should be taken into account. A literature review of the effects of other relevant molecules may also be useful. It is common practice to take into account a safety factor of ten to allow for species differences and inaccuracies to the calculation.

If the product(s) to be investigated in an exploratory clinical trial have a new mechanism of action or if they are biotechnology-derived products, the MABEL approach may be the safest possibility.

It should also be noted that in early phase trials and in particular for exploratory trials there may still be a relative lack of pharmacokinetic data. Therefore it may be difficult to calculate a MABEL value very precisely.



Whereas additional safety factors could be used to take into account such uncertainties it is generally not recommended that this would be done extensively as a substitute for achievable pre-clinical data outlined in earlier sections. First, it is not always clear what the safety factor should be to increase the original factor of 10. Using arbitrarily chosen factors is no guarantee that safety is indeed sufficiently safeguarded and may on the other hand quickly lead to unrealistically high safety factors. It may be more realistic in some cases to obtain the necessary data that could reduce the uncertainty and that would enable a more accurate extrapolation from animals to humans than to keep increasing the margin of safety.

Maximal dose

The estimation of maximal acceptable doses for exploratory clinical trials based on animal experiments was discussed in previous sections. Dose selection based on real exposure should be preferred where possible and otherwise scaling on a mg/m^2 basis should be done. The response observed in humans in previous cohorts during the exploratory clinical trial should be taken into account before dose escalations. Obviously, an adverse clinical response that occurs in clinical testing would mean that the maximally allowed exposure for an exploratory clinical trial has been reached. If a sufficient pharmacological response is observed that allows to answer the question that was the reason to undertake the exploratory trial, the maximally allowed dose should also be considered to have been reached. Escalation of the dose above any of these limits would generally not be acceptable in an exploratory clinical trial, unless the observed dose-limiting effects are reflecting an interaction with the primary pharmacological target. An escalation of the dose may then be acceptable on condition that the effects are not serious or severe, and that they are monitorable and reversible and furthermore such dose escalation should be necessary to answer the question that is decisive for the clinical development. It should also be considered that an effect that is dose limiting to normal volunteers may not be dose limiting for patients: therapeutic effects in the latter may be untoward in the former, sensitivity may be different between normal volunteers and patients, some mechanisms may play a role in the one and not in the other etc. Maximal acceptable doses may thus be dependent on the type of subjects.



General clinical and ethical requirements

The safety of participants in first-in-human trials can be improved by careful consideration of the risks associated with it and by pro-actively managing those risks. Because expCTA studies present fewer potential risks than do traditional phase I studies which look for dose-limiting toxicity, expCTA investigations in humans can be initiated with less and/or different pre-clinical support than is required for traditional CTA studies. Nevertheless, several key issues should be taken into account.

A. Study participants:

Subject intended to be enrolled into a clinical study should be appropriate for the specific questions addressed in the study. Depending on these questions, the subjects can be either healthy volunteers or patients, preferably with minimal disease and in stable condition. However, the approach can also be considered when developing products to treat serious diseases. Especially in serious diseases for which no satisfactory alternative therapies are available, appropriate flexibility should ensure that drug development is not delayed for these patients. 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 damage. In general, expCTA studies should not be performed in pediatric patients and pregnant or lactating women.

B. Site of the clinical trial

Although expCTA studies should present fewer potential risks than do traditional phase I studies, a thorough knowledge of existing guidelines on eIND/expCTA studies is required to be able to make a correct judgment of the risks involved and to evaluate the preclinical dossier in collaboration with the CA, EC and pharmaceutical company. Therefore, expCTA studies should only be performed by trained investigators who have acquired the necessary expertise in conducting early clinical drug trials (i.e. phase I-II) under well controlled circumstances. Expedited CTA studies should take place in well equipped clinical facilities and be conducted by medical staff with appropriate level of training and experience in early clinical drug development. Training in Good Clinical Practice (GCP), safety training and Basic Life Support should be considered mandatory for investigator and site personnel.



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End of the exploratory phase and initiation of further development

An exploratory clinical trial should try to answer a specific question or group of questions that will allow to decide on bringing one or more compounds to development or to further pursue a target in discovery and development research. This means that the investigational plan should be clearly outlined at the moment of submission, and clinical stopping points for each of the compounds or the target tested should be provided. When the original questions are answered the exploratory clinical trial should be ended. Amendments could be submitted within the context of an exploratory clinical trial if this is deemed necessary, but if these amendments are intended to extend the trial beyond the original objectives, this must first be discussed with the FAMHP and the EC that is concerned with the trial.

Once the decision can be taken to proceed with one or more compounds into formal development, this decision should be clearly communicated. Since an exploratory trial is designed to answer very specific questions with limited testing, it should be ascertained that the complete package of pre-clinical testing that would normally be expected to support development should be available before starting a development program. Obviously the data that were obtained during the exploratory phase can be used. For instance, since a 2-week toxicology study according to GLP has been conducted in rodents this study does not need to be repeated. Pre-clinical data that were obtained to support the exploratory trial may be completed to meet the requirements to support further development.



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List of abbreviations

ADME	Absorption, Distribution, Metabolism, Excretion
AUC	Area Under the Curve
CA	Competent Authority
C _{max}	Maximal plasma Concentration
CPD	Chemical and Pharmaceutical data
CTA	Clinical Trial Application
EC	Ethics Committee
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EudraCT	Database of all clinical trials commencing in the European Community (http://eudract.emea.europa.eu/)
expCTA	Exploratory Clinical Trial Application
eIND	Exploratory Investigational New Drug Application
FAMHP	Federal Agency for Medicinal and Health Products in Belgium
FANC	Federal Agency for Nuclear Control in Belgium
FDA	Food and Drug Administration in the US
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GRAS	Generally Recognised As Safe
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MABEL	Minimal Anticipated Biological Effect Level
MTD	Maximal Tolerated Dose
NIMP	Non-Investigational Medicinal Product
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Effect Level
PhEUR	European Pharmacopea
PET	Positron Emission Tomography
PK/PD	Pharmacokinetics/Pharmacodynamics



Summary of the pre-clinical requirements depending on the planned exploratory clinical trial.

Planned Exploratory Clinical Trial	Required pre-clinical information
<p>Maximum 5 administrations. Total dose < 100 µg. Each dose < 100th NOAEL and <100th pharmacologically active dose.</p> <p>Maximum 5 administrations. Each dose < 100 µg. Each dose < 100th NOAEL and <100th pharmacologically active dose.</p> <p>Repeat dose clinical trials up to 14 days. Starting dose: MABEL or 1/50th NOAEL. Maximal dose: resulting in human exposure = AUC at NOAEL in non-rodent or ½ AUC in rodent species.</p> <p>Repeat dose clinical trials up to 14 days. Starting dose: MABEL or 1/50th NOAEL. Maximal dose: determined by observed toxicity in animals or human exposure capped at 1/10th of animal exposure (AUC-based) at highest dose tested in case no toxicity is observed.</p>	<p>Extended single dose toxicity. Limit dose 10 mg/kg in rats. Early sacrifice group (2 days) is important and reversibility in the high dose group. Route of exposure is I.V. or intended clinical route and sufficient exposure should be guaranteed. Genotoxicity generally not required. Appropriate in vitro profiling. 7-day repeat dose toxicology including toxicokinetic and histopathological assessment. Route of exposure is I.V. or intended clinical route. Pharmacological characterisation in a relevant species. AMES-test or appropriate alternative. Appropriate in vitro profiling. 2-week repeat dose toxicology study. Confirmatory study with duration at least the intended clinical duration in a non-rodent. Safety pharmacology studies that could be combined with toxicological studies. AMES test and an in vitro test for chromosomal damage or in vivo micronucleus test (MTD in rodent toxicology testing) Safety pharmacology studies that could be combined with toxicological studies. 2-week toxicology study in a rodent and a non-rodent. If no toxicity is observed in animals, the limit dose should result in an AUC that is 10-fold the intended human exposure. Safety pharmacology studies that could be combined with toxicological studies and with same limit dose. Genotoxicity testing conform ICH S2. Safety pharmacology studies that could be combined with toxicological studies.</p>