図1. 探索的臨床試験治験薬と法規制 (1)

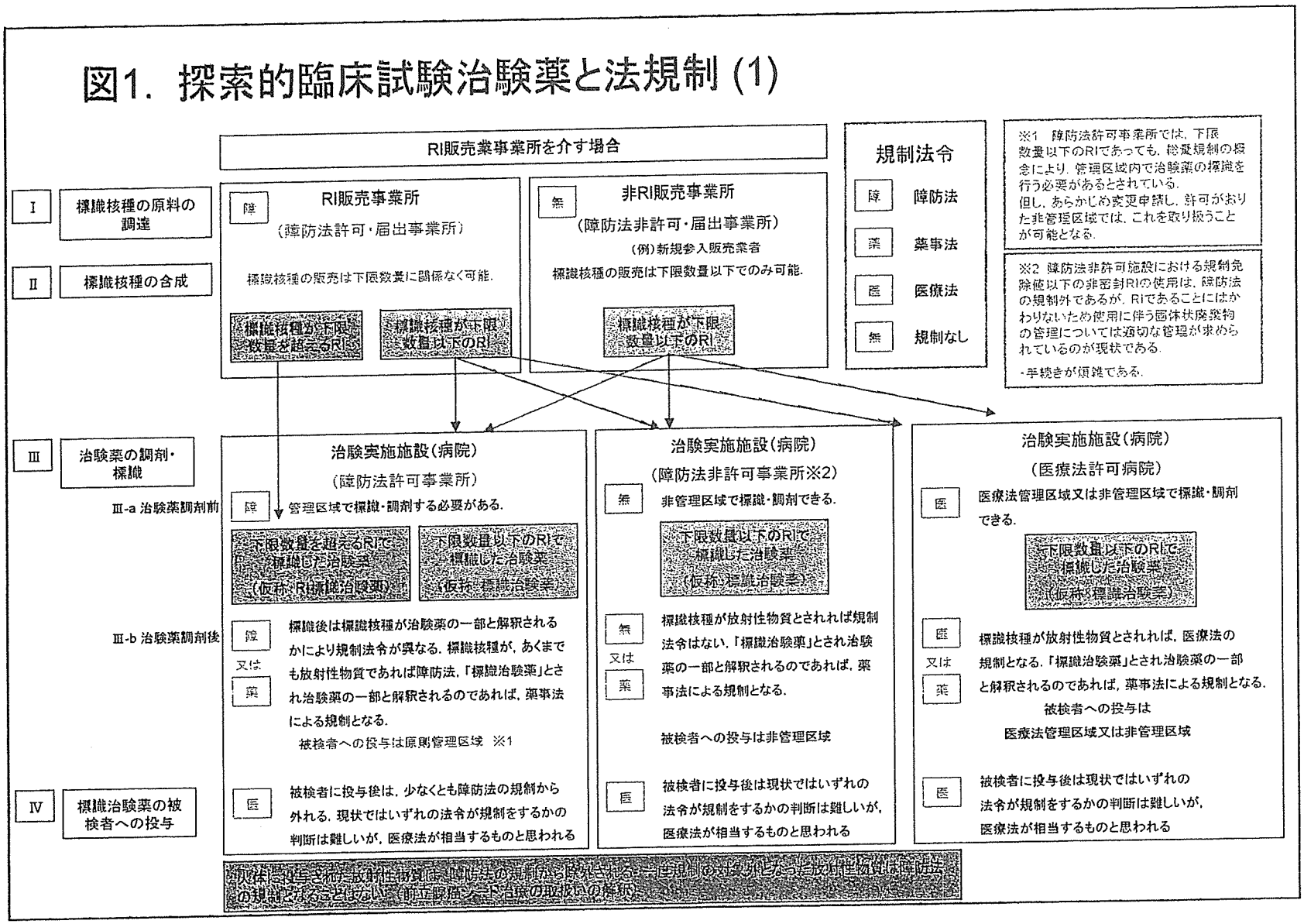

図2. 探索的臨床試験治験薬と法規制 (2)

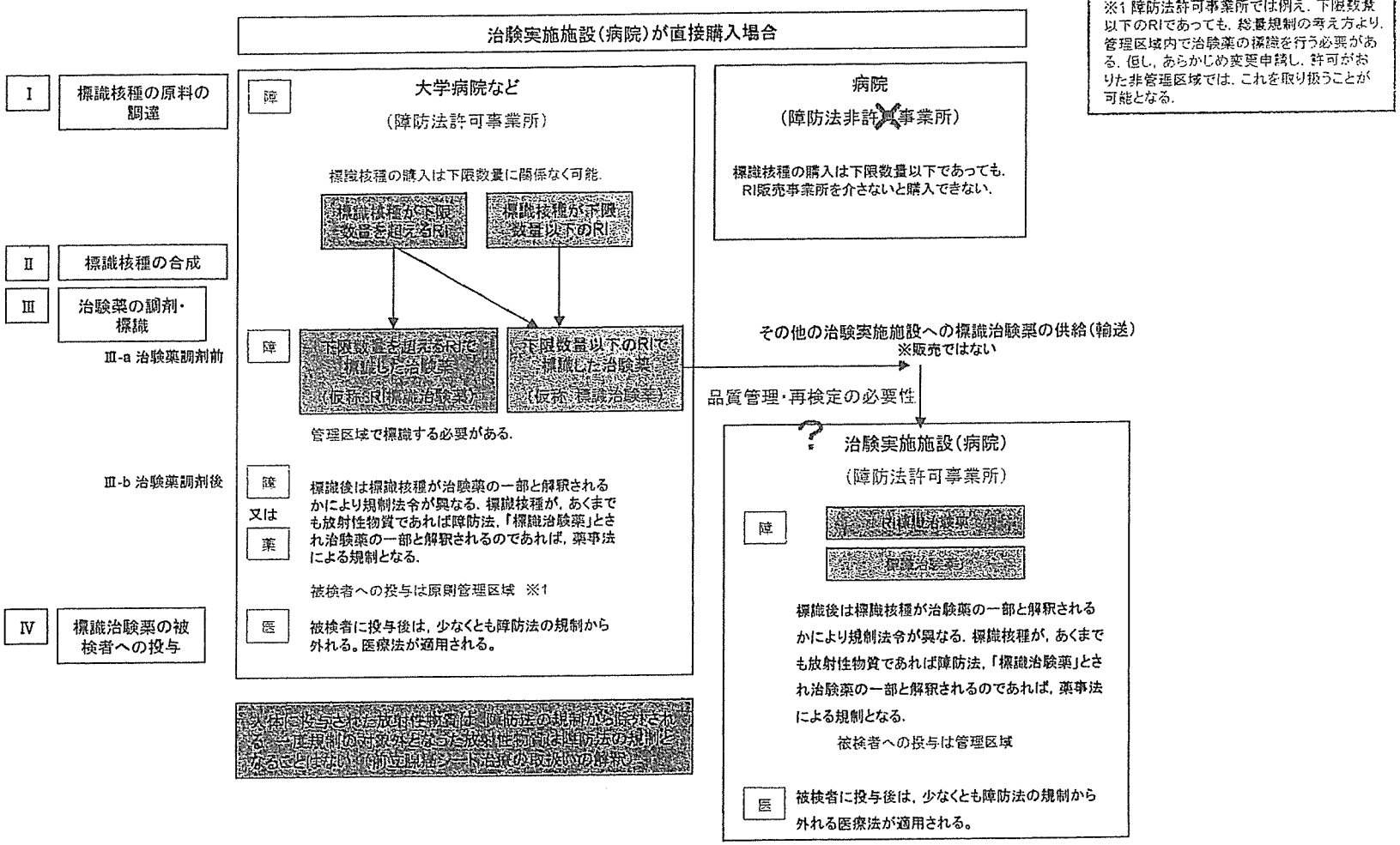

図3. 探索的臨床試験治験薬と法規制 (3)

		下限数量を超えるRIで標識した治験薬 (仮称：RI標識治験薬)	下限数量以下のRIで標識した治験薬 (仮称：標識治験薬)
		障	
V	標識治験薬等の廃棄	障防法許可事業所では，余剰分のRI標識治験薬，標識治験薬ともに管理区域内にて廃棄する必要がある．液体のものは管理区域内の排水への廃棄が可能である．固体のものについては放射性廃棄物として廃棄することになる．	
			障防法非許可事業所では，液体のものは一般排水への廃棄が可能である．固体のものについては，産業廃棄物として廃棄することが合理的である．
		医	
VI	検体(血液，尿，便，組織片)の採取	RI標識治験薬の場合，検体の採取場所は，治験実施施設(病院)の管理区域で行われることも考慮される．被検者に投与された放射能量により判断する必要がある． 検体採取に使用した器具等で廃棄する固体の物は，放射性廃棄物として取り扱う． 本事項を規制する法令は，人体投与後であるため，医療法が適用される．	検体の採取場所は，治験実施施設(病院)であれば管理区域，非管理区域は法令上は問われない．但し，ごく微量な放射能を有する被検者を，それ以上の放射線被ばくを受ける可能性のある管理区域内で検体採取するのは合理的とは言えない． 検体採取に使用した器具等で廃棄する固体の物は，医療廃棄物として取り扱うことが望ましい． 本事項を規制すべき法令は，人体投与後であるため，医療法が適切と思われる．
VII	検体の輸送	採取された検体は，場合によっては放射性物質として取り扱う必要があることも想定される．	採取された検体は，放射性物質として取り扱う必要はないと思われる．
VIII	検体の廃棄	解析に使用しなかった検体の廃棄については，医療廃棄物として取り扱うことが適切と思われる．	解析に使用しなかった検体の廃棄については，医療廃棄物として取り扱うことが適切と思われる．

研究成果の刊行に関する一覧表

書籍

該当なし

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
杉山雄一、栗原千絵子、馬屋原宏、須原哲也、池田敏彦、伊藤勝彦、矢野恒夫、三浦慎一、西村伸太郎、大塚峯三、小野俊介、大野泰雄	マイクロドーズ臨床試験の実施基盤　―指針作成への提言―	臨床評価	33	649-677	2006
大野泰雄ら	マイクロドージング試験の毒性学的根拠について．マイクロドーズ臨床試験　理論と実践―新たな創薬開発ツールの活用に向けて	じほう	杉山雄一、栗原千絵子編	11-22	2007
杉山雄一，栗原千絵子，矢野恒夫，馬屋原　宏，残華淳彦，熊谷雄治，西村伸太郎，伊藤勝彦，谷内一彦，加藤基浩，井上登美夫，鈴木和年，須原哲也，池田敏彦（マイクロドーズ・探索臨床試験研究会有志	指針作成の提言と論点提示．In：杉山雄一，栗原千絵子編著．マイクロドーズ臨床試験：理論と実践－新たな創薬開発ツールの活用に向けて－	じほう	杉山雄一、栗原千絵子編	315-339	2007
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The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 23 January 2003
CPMP/SWP/2599/02

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POSITION PAPER ON NON-CLINICAL SAFETY STUDIES TO SUPPORT CLINICAL TRIALS WITH A SINGLE MICRODOSE

DISCUSSION IN THE SAFETY WORKING PARTY	June 2002
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DISCUSSION OF COMMENTS BY THE SAFETY WORKING PARTY	October 2002
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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.eu.int http://www.emea.eu.int

POSITION PAPER ON NON-CLINICAL SAFETY STUDIES TO SUPPORT CLINICAL TRIALS WITH A SINGLE MICRODOSE

1 INTRODUCTION

Non-clinical safety studies to support the conduct of human clinical trials for pharmaceuticals has been internationally harmonised by the International Conference on Harmonisation as outlined in International Conference on Harmonisation (ICH) Topic M3: Note for Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, Topic S7A: Note for Guidance on Safety Pharmacology Studies for Human Pharmaceuticals and Topic S7B: Note for Guidance on Safety Pharmacology Studies for assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals. However, different regional requirements still exist with regard to non-clinical studies to support the first dose to humans.

2 SCOPE

This Position Paper defines common standards of the non-clinical safety studies needed to support human clinical trials of a single dose of a pharmacologically active compound using microdose techniques.

In the current context, the term "microdose" is defined as less than $1/100^{th}$ of the dose calculated to yield a pharmacological effect of the test substance based on primary pharmacodynamic data obtained *in vitro* and *in vivo* (typically doses in, or below, the low microgram range) and at a maximum dose of ≤ 100 microgram. An example of such a clinical trial is the early characterisation of a substance's pharmacokinetic- / distribution properties or receptor selectivity profile using positron emission tomography (PET) imaging, accelerator mass spectrometry (AMS) or other very sensitive analytical techniques.

The clinical trials covered by this Position Paper will be exploratory in nature (pre - phase I) and may be conducted with a single test substance or with a number of closely related pharmaceutical candidates to choose the preferred candidate or formulation for further development. In any case the total amount of test compound(s) administered should not exceed 100 micrograms.

The non-clinical safety testing should be sufficient to assess the safety of clinical trial participants and patients in line with the requirements outlined in the Helsinki Declaration. However, the extent of required studies should be proportionate to the nature and scope of the clinical trial. Therefore the CPMP proposes that certain deviations from the existing CPMP/ICH notes for guidance to support pre-phase I clinical trials may be scientifically justified.

3 OVERVIEW OF EXISTING GUIDANCE FOR NON-CLINICAL SAFETY STUDIES TO SUPPORT SAFETY IN FIRST HUMAN CLINICAL TRIALS OF NEW PHARMACEUTICAL CANDIDATES

Non-clinical studies to support human clinical trials have been harmonised (see Introduction); regional differences still exist regarding non-clinical testing to support the first dose to humans. In the European Union, repeated dose toxicity studies in two species (one non-rodent) for a minimum duration of 2 weeks are required to support a single, first human dose. However, in the United States of America, single dose acute toxicity studies are in some cases considered sufficient to support a single dose human clinical trial.

In 1996, the FDA published a notice on single dose acute toxicity studies for pharmaceuticals that would allow for the use of single-dose toxicity studies to support single dose studies in humans.

ICH M3 includes a requirement for safety pharmacology studies, which is detailed further in the ICH S7A guideline and guidance on the assessment of QT interval prolongation by non-cardiovascular medicinal products is given in the ICH S7B guideline.

For biotechnology-derived medicinal products, the safety assessment should be considered on a case-by-case basis, which would also apply to single microdose human clinical trials. Guidance is given in ICH Topic S6.

For anticancer medicinal products, guidance for non-clinical evaluation before first human dose is given in the CPMP Note for Guidance on the Pre-clinical Evaluation of Anticancer Medicinal Products.

4 RECOMMENDATIONS

4.1 EXTENDED SINGLE-DOSE TOXICITY STUDY AND OTHER EFFECTS ON VITAL ORGAN FUNCTION

The ICH M3 recommendation is for safety pharmacology, single dose toxicity studies and repeated dose toxicity studies. This set of studies may be replaced by an extended single-dose toxicity study in only one mammalian species if the choice of species could be justified based on comparative in vitro metabolism data and by comparative data on in vitro primary pharmacodynamics / biological activity.

The extended single-dose toxicity study should include a control group, and a sufficient number of treatment groups to allow the establishment of the dose inducing a minimal toxic effect. For compounds with low toxicity a limit dose approach could be used. Allometric scaling from animal species to man[1] and using a safety factor of 1000 should be used to set the limit dose. If a toxic effect is observed at the limit dose, the non-toxic dose level should be established.

The number of animals should be sufficient to ensure reliable interpretation of the study results. The use of both genders should be considered. The extended single-dose toxicity study should be designed to obtain the maximum amount of information from the smallest number of animals. Two routes of administration should generally be used, the intravenous as well as the intended clinical route, which would also allow assessment of local tolerance. When intravenous dosing is the route of administration in humans, this route alone in animal testing would generally be sufficient.

The study period should be 14 days and include an interim sacrifice on Day 2 (day of dosing defined as Day 1). All mortalities should be recorded. Time of onset, duration, and reversibility of toxicity and clinical observations should be recorded. Gross necropsy should be performed on all animals, including those sacrificed moribund, found dead, or terminated at Days 2 and 14. .

The extended single-dose toxicity study should be designed to obtain information on haematology and clinical chemistry at a minimum of two time points (Days 2 and 14) and histopathology.

Information should also be obtained on any other organ system where the test substance localises and e.g., those organ systems intended to be visualised by imaging agents.

In addition, all available background information on the test substance and/or close pharmaceuticals as well as on the therapeutic class with respect to vital organ function and other safety parameters obtained in drug screening should be provided. Examples of such data are receptor screening profiles, activity at HERG and other ion channels, effect on action potentials, behavioural screens etc.

4.2 GENOTOXICITY STUDIES

In vitro genotoxicity studies should be performed as recommended in relevant ICH guidance.

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[1] See CPMP/ICH/283/95 for factors in allometric scaling

However, if a test substance belongs to a well-known chemical class for which genotoxicity data are available on other class representatives, performance of abridged/reduced versions of mutation test in bacteria (Ames test) and chromosome aberration, mouse lymphoma or in vitro micronucleus tests may be sufficient. If abridged/reduced versions of genotoxicity tests are used, data demonstrating that the modification is scientifically justified and provides valid data should be provided. If an equivocal or positive finding is obtained, additional testing should be performed.

4.3 LOCAL TOLERANCE STUDIES

Local tolerance studies may not be needed when the clinical route of administration is used in the extended single-dose toxicity study.

5 FINAL REMARKS

With respect to radiopharmaceuticals, the corresponding stable isotope test substance should be used for both the extended single-dose toxicity study and the genotoxicity studies.

Before entry into man, adequate information should be available on the primary pharmacodynamics of each test substance in the screening programme, e.g., when a number of structural analogues are included in the screening programme.

A sponsor should always ensure that an appropriate safety assessment is performed before entry into humans. If toxicity is observed, this may need to be clarified by additional investigations before entry into humans. Margins of safety and type of toxicity observed should be assessed.

All non-clinical safety studies should be conducted in accordance with the principles of Good Laboratory Practice (GLP).

The reduced/abbreviated testing (as compared to the ICH guidance M3, S7Aand S7B) outlined above is not sufficient to support clinical trial situations with escalating dose regimes or higher doses / exposures than indicated above. Guidance for such trials is found in the ICH M3, S7A and S7B.
The non-clinical safety assessment of biotechnology-derived products should be considered on a case-by-case basis as outlined in ICH Topic S6. Guidance for non-clinical testing of anti-cancer medicinal products is given in the CPMP Note for Guidance on the Pre-clinical Evaluation of Anti-cancer Medicinal Products. The extended single-dose toxicity study approach and the recommendation for genotoxicity studies given in this Position Paper may not be relevant for these product categories.

Guidance for Industry, Investigators, and Reviewers

Exploratory IND Studies

(PDF version of this document)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2006

Pharmacology/Toxicology

Guidance for Industry, Investigators, and Reviewers
Exploratory IND Studies

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573

http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
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Pharmacology/Toxicology

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ATTACHMENT

Guidance for Industry and Reviewers[1]
Exploratory IND Studies

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. Alternative approaches can be used if the approach satisfies the requirements of the applicable statutes and regulations. Discussions of an alternative approaches can be scheduled by contacting the FDA staff responsible for implementing this guidance. If the appropriate FDA staff cannot be located, contact can be made using the telephone number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to clarify what preclinical and clinical approaches, as well as chemistry, manufacturing, and controls information, should be considered when planning exploratory studies in humans, including studies of closely related drugs or therapeutic biological products, under an investigational new drug (IND) application (21 CFR 312). Existing regulations allow a great deal of flexibility in the amount of data that needs to be submitted with an IND application, depending on the goals of the proposed investigation, the specific human testing proposed, and the expected risks. The Agency believes that sponsors have not taken full advantage of that flexibility and often provide more supporting information in INDs than is required by regulations. This guidance is intended to clarify what manufacturing controls, preclinical testing, and clinical approaches can be considered when planning limited, early exploratory IND studies in humans.

For the purposes of this guidance the phrase *exploratory IND study* is intended to describe a clinical trial that

- is conducted early in phase 1
- involves very limited human exposure, and
- has no therapeutic or diagnostic intent (e.g., screening studies, microdose studies).

Such exploratory IND studies are conducted prior to the traditional dose escalation, safety, and tolerance studies that ordinarily initiate a clinical drug development program. The duration of dosing in an exploratory IND study is expected to be limited (e.g., 7 days). This guidance applies to early phase 1 clinical studies of investigational new drug and biological products that assess feasibility for further development of the drug or biological product.[2]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In its March 2004 *Critical Path Report*,[3] the Agency explained that to reduce the time and resources expended on candidate products that are unlikely to succeed,[4] new tools are needed to distinguish earlier in the process those candidates that hold promise from those that do not. This guidance describes some early phase 1 exploratory approaches that are consistent with regulatory requirements while maintaining needed human subject protection, but that involve fewer resources than is customary, enabling sponsors to move ahead more efficiently with the development of promising candidates.

A. Traditional Phase 1 Approach

Typically, during pharmaceutical development, large numbers of molecules are generated with the goal of identifying the most promising candidates for further development. These molecules are generally structurally related, but can differ in important ways. Promising candidates are often selected using in vitro testing models that examine binding to receptors, effects on enzyme activities, toxic effects, or other in vitro pharmacologic parameters; these tests usually require only small amounts of the drug. Candidates that are not rejected during these early tests are prepared in greater quantities for in vivo animal testing for efficacy and safety. Commonly, a single candidate is selected for an IND application and introduction into human subjects, initially healthy volunteers in most cases.

Before the human studies can begin, an IND must be submitted to the Agency containing, among other things, information on any risks anticipated based on the results of pharmacologic and toxicological data collected during studies of the drug in animals (21 CFR 312.23(a)(8)). These basic safety tests are most often performed in rats and dogs. The studies are designed to permit the selection of a safe starting dose for humans, to gain an understanding of which organs may be the targets of toxicity, to estimate the margin of safety between a clinical and a toxic dose, and to predict pharmacokinetic and pharmacodynamic parameters. These early tests are usually resource intensive, requiring significant investment in product synthesis, animal use, laboratory analyses, and time. Many resources are invested in, and thus wasted on, candidate products that subsequently are found to have unacceptable profiles when evaluated in humans — less than 10 percent of INDs for new molecular entities (NME) progress beyond the investigational stage to submission of a marketing application (NDA).[3] In addition, animal testing does not always predict performance in humans, and potentially effective candidates may not be developed because of resource constraints.

Existing regulations allow a great deal of flexibility in terms of the amount of data that need to be submitted with any IND application, depending on the goals of the proposed investigation, the specific human testing proposed, and the expected risks. The Agency believes that sponsors have not taken full advantage of that flexibility. As a result, limited, early phase 1 studies, such as those described in this guidance, are often supported by a more extensive preclinical database than is required by the regulations.

This guidance describes preclinical and clinical approaches, and the chemistry, manufacturing, and controls information that should be considered when planning exploratory IND studies in humans, including studies of closely related drugs or therapeutic biological products, under a single IND application (21 CFR 312).

B. Exploratory IND Approach

Exploratory IND studies usually involve very limited human exposure and have no therapeutic or diagnostic intent. Such studies can serve a number of useful goals. For example, an exploratory IND study can help sponsors

- Determine whether a mechanism of action defined in experimental systems can also be observed in humans (e.g., a binding property or inhibition of an enzyme)
- Provide important information on pharmacokinetics (PK)
- Select the most promising lead product from a group of candidates[5] designed to interact with a particular therapeutic target in humans, based on PK or pharmacodynamic (PD) properties
- Explore a product's biodistribution characteristics using various imaging technologies

Whatever the goal of the study, exploratory IND studies can help identify, early in the process, promising candidates for continued development and eliminate those lacking promise. As a result, exploratory IND studies may help reduce the number of human subjects and resources, including the amount of candidate product, needed to identify promising drugs. The studies discussed in this guidance involve dosing a limited number of subjects with a limited range of doses for a limited period of time.

Existing regulations provide more flexibility with regard to the preclinical testing requirements for exploratory IND studies than for traditional IND studies. However, sponsors submitting the kinds of studies described in this guidance have not always taken full advantage of that flexibility. Sponsors often provide more supporting information in their INDs than is required by the regulations. Because exploratory IND studies involve administering either sub-pharmacologic doses of a product, or doses expected to produce a pharmacologic, but not a toxic, effect, the potential risk to human subjects is less than for a traditional phase 1 study that, for example, seeks to establish a maximally tolerated dose. ***Because exploratory IND studies present fewer potential risks than do traditional phase 1 studies that look for dose-limiting toxicities, such limited exploratory IND investigations in humans can be initiated with less, or different, preclinical support than is required for traditional IND studies.***[6]

The Agency expects that this early phase 1 exploratory IND approach will apply to a number of different study paradigms. Although his guidance explores several potential applications, many others can be proposed. The Agency believes that, consistent with its Critical Path Initiative, clarifying Agency thinking about how much and what kind of testing is needed to support early studies in humans will facilitate the entry of new products into clinical testing and speed product development.

Although exploratory IND studies may be used during development of products intended for any indication, it is particularly important for manufacturers to consider this approach when developing products to treat serious diseases. Because the approach can help identify promising candidates more quickly and precisely, exploratory IND studies could become an important part of the armamentarium when developing drug and biological products to treat a serious or life-threatening illness. The Agency has previously articulated its commitment to ensuring that appropriate flexibility is applied when patients with a serious disease and no satisfactory alternative therapies are enrolled in a trial with therapeutic intent.[7]

III. CONTENT OF IND SUBMISSIONS

To begin any kind of testing in humans, applicants must submit an IND application to the Agency with certain types of information (see 21 CFR 312.23 IND Content and Format). The primary purpose of the IND submission is to ensure that subjects will not face undue risk of harm. The major information that must be submitted includes:

- Information on a clinical development plan
- Chemistry, manufacturing, and controls information
- Pharmacology and toxicology information
- Previous human experience with the investigational candidate or related compounds, if there is any

The following sections discuss the first three in more detail. Because the exploratory IND studies addressed by this guidance will be first in human studies, previous human experience is not pertinent and will not be discussed. The common theme throughout is that, depending on the study, the informational requirements for exploratory IND studies are more flexible than for traditional IND studies.

A. Clinical Information

1. Introductory statement and general investigational plan

A traditional IND application describes the rationale for the proposed clinical trial program and discusses the potential outcome of the clinical investigation. The exploratory IND studies discussed here focus on a circumscribed study or group of studies, and plans for further development cannot be formulated without the results of these studies. Therefore, an exploratory IND application should articulate the rationale for selecting a compound (or compounds) and for studying them in a single trial or related trials, as this represents all that is known about the overall development plan at this stage. This section should also make it clear that the IND is intended to be withdrawn[8] after completion of the outlined study or studies.

2. *Types of studies*

Potentially useful study designs include both single- and multiple-dose studies. In single-dose studies, a sub-pharmacologic[9] or pharmacologic dose is administered to a limited number of subjects (healthy volunteers or patients). For example, microdose studies usually involve the single administration of a small dose with the goal of collecting pharmacokinetic information or performing imaging studies, or both.

Repeat dose clinical studies can be designed with pharmacologic or pharmacodynamic endpoints. In exploratory IND studies, the duration of dosing should be limited (e.g., 7 days). For escalating dose studies done under an exploratory IND, dosing should be designed to investigate a pharmacodynamic endpoint, not to determine the limits of tolerability.

B. Chemistry, Manufacturing, and Controls Information

The regulations at 21 CFR 312.23(a)(7)(i) emphasize the graded nature of chemistry, manufacturing, and controls (CMC) information needed as development under an IND application progresses. Although in each phase of a clinical investigational program sufficient information should be submitted to ensure the proper identification, strength, quality, purity, and potency of the investigational candidate, the amount of information that will provide that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information already available. For the purpose of an exploratory IND application, the CMC information indicated below can be provided in a summary report to enable the Agency to make the necessary safety assessment.

The sponsor must state in the beginning of the exploratory IND application whether it believes the chemistry or manufacturing of the candidate product presents any potential for human risk (e.g., specific findings in preclinical studies associated with known risks of related compounds) (§ 312.23). If so, these potential risks should be discussed, and the steps proposed to monitor for such risks should be described.

The Agency is in the process of developing guidance explaining the stepwise approach to meeting current good manufacturing practice (CGMP) regulations. Once finalized, that guidance will be useful to persons seeking to manufacture, or prepare, products intended for use in an exploratory IND study.

1. General information for the candidate product

Except as noted below, the extent and type of chemistry and manufacturing information to be submitted in an exploratory IND application is similar to that described in current guidance for use of investigational products.[10] Information on each candidate product (i.e., the active ingredient) can be submitted in a summary report containing the following items.

- Description of the candidate product, including physical, chemical, and/or biological characteristics, as well as its source (e.g., synthetic, animal source, plant extract, or biotechnology-derived) and therapeutic class (e.g., radiopharmaceutic, immunosuppressant, agonist, antagonist) (see sections below for exceptions).
- Description of the dosage form and information related to the dosage form
- Description of the formulation or routes of administration intended to be used in the human trial. For oral administration, sponsors can consider using suspensions or solutions in addition to the more usual tablets, powders, and capsules. For products intended for ophthalmic, inhalational (aqueous base), or parenteral administration, sterility and apyrogenicity must be ensured. For biological candidate products, freedom from contaminants associated with their manufacture, such as viruses, mycoplasma, and foreign DNA, also should be ensured. All excipients should be generally recognized as safe[11] or part of a formulation that is approved or licensed in the United States for the same route of administration and amount,[12] or adequately qualified through appropriate animal studies.

- The grade and quality (e.g., USP, NF, ACS) of excipients used in the manufacture of the investigational candidate product, including both those components intended to appear in the product and those that may not appear, but that are used in the manufacturing process

- Name and address of the manufacturer(s) (if different from the sponsor)

- The method of preparation of the candidate product lots used in preclinical studies and intended for the proposed human study, including a brief description of the method of manufacture and the packaging procedure, as appropriate, with a description of the container and closure system. For the active substance, include a list of the starting materials, reagents, solvents, catalysts used, and purification steps employed to prepare the candidate product. For sterile products, describe the sterilization process and controls for ensuring sterility. For biological/biotechnology-derived products, also identify the source material (e.g., Master Cell Bank), describe the expression system (e.g., fermentation methods) and harvest methods, as well as methods for removal/inactivation of potential viral contaminants. We recommend the use of a detailed flow diagram that includes all materials used as the usual, most effective, presentation of this information.

- Quantitative composition of the product

- A brief description of adequate test methods used to ensure the identity, strength, quality, purity, and potency accompanied by the test results, or a certificate of analysis, of the candidate product lots used in toxicological studies and intended for the proposed human study. For biotechnology products produced in mammalian cells or animals, this will include tests and studies to ensure the removal and/or inactivation of potential viral contaminants.

- Information that demonstrates the stability of the product during toxicology studies and an explanation of how stability will be evaluated during the clinical studies

- For ophthalmic, inhalational (aqueous base), or parenteral dosage forms, results from sterility and pyrogenicity tests

2. *Analytical characterization of candidate product*

There are two scenarios under which CMC information can be provided to an IND application. In the first scenario, the ***same batch*** of candidate product is used in both the toxicology studies and clinical trials. This material will be qualified for human use based on the CMC information (see III.B.1, above) and results of the toxicology studies described elsewhere in this guidance. Although we recommend establishing the impurity profile to the extent possible for future reference and/or comparison, not all impurities of the candidate product may need characterization at this stage of product development. If an issue arises during the toxicology qualification of the product, the appropriate parameters can be studied further, on an as-needed basis. Impurities (e.g., chemical and microbiological) should be characterized in accordance with recommendations in Agency guidance,[13] if, and when, the sponsor files a traditional IND for further clinical investigation.

In the second scenario, the batch of candidate drug product to be used in the clinical studies may not be the same as that used in the nonclinical toxicology studies. In such a case, the sponsor should demonstrate by analytical testing that the batch to be used is ***representative*** of batches used in the nonclinical toxicology studies. To achieve this, relevant analytical quality test results should be sufficient to enable comparison of different batches of the product. Tests to accomplish this include:

- Identity
- Structure (e.g., optical rotation (for chiral compounds), reducing/non-reducing electrophoresis (for proteins))
- Assay for purity
- Impurity profile (e.g., product- and process-related impurities, residual solvents, heavy metals)
- Assay for potency (biologic)
- Physical characteristics (as appropriate)
- Microbiological characteristics (as appropriate)

C. Safety Program Designs — Examples

Pharmacology and toxicology information is derived from preclinical safety testing performed in animals and in vitro. Preclinical studies for small molecules are described in ICH M3 while those for biologics follow guidance described in ICH S6. Some of the toxicology tests described in this guidance may not be appropriate for biologics. The toxicology evaluation recommended for an exploratory IND application is more limited than for a traditional IND application.[14] The basis for the reduced preclinical package is the reduced scope of an exploratory IND clinical study. Although exploratory IND studies in some cases are expected to induce pharmacologic effects, they are not designed to establish maximally tolerated doses. Furthermore, the duration of drug exposure in exploratory IND studies is limited. The level of preclinical testing performed to ensure safety will depend on the scope and intended goals of the clinical trials.

There are a number of study objectives for which the preclinical safety programs may be tailored to the study design. Examples include: confirming that an expected mechanism of action can be observed in humans; measuring binding affinity or localization of drug; assessing PK and metabolism; comparing the effect on a potential therapeutic target with other therapies. Three examples are discussed in detail in the following paragraphs.

1. Clinical studies of pharmacokinetics or imaging

Microdose studies are designed to evaluate pharmacokinetics or imaging of specific targets and are designed not to induce pharmacologic effects. Because of this, the risk to human subjects is very limited, and information adequate to support the initiation of such limited human studies can be derived from limited nonclinical safety studies. A microdose is defined as less than 1/100th of the dose of a test substance calculated (based on animal data) to yield a pharmacologic effect of the test substance with a maximum dose of ≤100 micrograms (for imaging agents, the latter criterion applies).[15] Due to differences in molecular weights as compared to synthetic drugs, the maximum dose for protein products is ≤30 nanomoles.

FDA currently accepts the use of extended single-dose toxicity studies in animals to support single-dose studies in humans. For microdose studies, a single mammalian species (both sexes) can be used if justified by in vitro metabolism data and by