# Guidance for Industry, Investigators, and Reviewers

# Exploratory IND Studies

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

**January 2006**
**Pharmacology/Toxicology**

*Contains Nonbinding Recommendations*

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# Exploratory IND Studies

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# Guidance for Industry and Reviewers[1]

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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).

[1] This guidance was developed by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER).

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collection of information in this guidance has been approved under OMB Control No. 0910-0014.

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

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[2] Specifically, this guidance is limited to drug and certain well-characterized therapeutic biological products (e.g., recombinant therapeutic proteins and monoclonal antibodies) regulated by CDER. The guidance does not apply to human cell or tissue products, blood and blood proteins, vaccines, or to products regulated as devices.

[3] *Innovation or Stagnation, Challenge and Opportunity on the critical Path to New Medical Products* (March 2004).

[4] "A new medical compound entering phase 1 testing, often representing the culmination of upwards of a decade of preclinical screening and evaluation, is estimated to have only an 8 percent chance of reaching the market," *Critical Path Report*, March 2004.

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

[5] For the purposes of this guidance, the term *candidate*, or *candidate product*, is used to describe a drug or biologic that is being tested in early exploratory studies under an IND. This guidance ***does not*** distinguish between a *drug product* and a *drug substance* as some other Agency guidances do.

(Most guidances use the term *drug product* to refer to a finished dosage form (e.g., tablet, capsule, solution) that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients, or a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo. *Drug substance* usually refers to any component that is intended to furnish pharmacological activity or other direct effect

- 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]

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in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body.)

[6] Generally, these types of studies would not be carried out in pediatric patients or in pregnant or lactating women.

[7] Subpart H Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses. See also FDA guidance for industry *Fast Track Drug Development Programs — Designation, Development, and Application Review*.

## 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.

[8] The withdrawn, or inactive, IND can be referenced in any subsequent traditional IND.

[9] A radiolabeled candidate compound can be administered at doses that are known to have no pharmacologic effect in humans without an IND application in basic research studies when the compound has previously been studied in humans and the results published in the literature. These basic research investigations are conducted under the oversight of an institutional review board (IRB) and a radioactive drug research committee (21 CFR 361.1).

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

[10] See guidance for industry *Content and Format of Investigational New Drug Applications for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products.*

- 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

[11] Excipients considered to be generally recognized as safe (GRAS) are included in a list that is maintained on the Internet at http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. See also 21 CFR 330.1, which explains the GRAS concept.

[12] Novel excipients should be appropriately qualified for their intended use. FDA has issued guidance on *Nonclinical Studies for Development of Pharmaceutical Excipients*.

- 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

[13] See footnote 10 and guidance for industry, *INDs for Phase 2 and Phase 3 Studies, Chemistry, Manufacturing, and Controls Information.*

[14] International Conference on Harmonisation (ICH) guidance for industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* describes what is expected for a traditional IND.

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 $1/100^{th}$ 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 comparative data on in vitro pharmacodynamic effects. The route of exposure in animals should be by the intended clinical route. In these studies, animals should be observed for 14 days post-dosing with an interim necropsy, typically on day 2, and endpoints evaluated should include body weights, clinical signs, clinical chemistries, hematology, and histopathology (high dose and control only if no pathology is seen at the high dose). The study should be designed to establish a dose inducing a minimal toxic effect, or alternatively, establishing a margin of safety. To establish a margin of safety, the sponsor should demonstrate that a large multiple (e.g., 100X) of the proposed human dose does not induce adverse effects in the experimental animals. Scaling from animals to humans based on body surface area can be used to select the dose for use in the clinical trial. Scaling based on pharmacokinetic/pharmacodynamic modeling would also be appropriate if such data are available.

Because microdose studies involve only single exposures to microgram quantities of test materials and because such exposures are comparable to routine environmental exposures, routine genetic toxicology testing is not needed. For similar reasons, safety pharmacology studies are also not recommended.

[15] See European Medicines Agency (EMEA), Evaluation of Medicines for Human Use, "Position Paper on Non-Clinical Safety Studies to Support Clinical Trials with a Single Microdose," CPMP/SWP/2599/02Rev 1, 23 June 2004.

*2. Clinical trials to study pharmacologically relevant doses*

A second example involves clinical trials designed to study pharmacologic effects of candidate products. More extensive preclinical safety data would be needed to support the safety of such studies. However, since the goal would not include defining a maximally tolerated dose, the evaluation can still be less extensive than typically needed to support a traditional IND application. See the flow chart in the Attachment to this document.

Repeat dose clinical trials lasting up to 7 days can be supported by a 2-week repeat dose toxicology study in a sensitive species accompanied by toxicokinetic evaluations. The goal of such a study would be to select safe starting and maximum doses for the clinical trial. The rat is the usual species chosen for this purpose, but other species might be selected. In addition to studies in a rodent species, additional studies in nonrodents, most often dogs, can be used to confirm that the rodent is an appropriately sensitive species. If it is known that a particular species is most appropriate for a class of compounds, studies can be limited to that species. This confirmation can be approached in a number of ways. A lack of gender difference in the rodent study can serve as a basis for testing only a single sex in the second species if only a single sex will be studied in the clinical trial.

The numbers of animals used in the confirmatory study can be fewer than normally used to attain statistically meaningful comparisons, but of sufficient number to rule out any toxicologically significant difference in sensitivity compared with rodent (e.g. four non-rodents per treatment group). The confirmatory study could be a dedicated study involving repeat administrations of a single dose level approximating the rat NOAEL[16] calculated on the basis of body surface area. Alternatively, the test in the second species could be incorporated as part of an exploratory, dose escalating study culminating in repeated doses equivalent to the rat NOAEL. The number of repeat administrations at the rat NOAEL should, at a minimum, be equal to the number of administrations, given with the same schedule, intended clinically. The route of administration should be the same as the expected clinical route, and toxicokinetic measurements should be used to assess exposure. The same endpoints assessed in the rodent study should be evaluated in the second species. If the data from the confirmatory study suggest that the rodent is not the more sensitive species, a 2-week repeated dose toxicity study should be performed in the second species to select doses for human trials. This study should include measurements of body weight, clinical signs, clinical chemistries, hematology, and histopathology.

In contrast to microdose studies, for clinical trials designed to evaluate higher or repeated doses, each candidate product to be tested should be evaluated for safety pharmacology.[17] Evaluation of the central nervous and respiratory systems can be performed as part the rodent toxicology studies while safety pharmacology for the cardiovascular system can be assessed in the nonrodent species, generally the dog, and can be conducted as part of the confirmatory or dose-escalation study.

[16] No-observed-adverse-effect level (NOAEL).

[17] For details see the guidance for industry *S7A Safety Pharmacology Studies for Human Pharmaceuticals*.

In general, each product in this type of exploratory IND should be tested for potential genotoxicity unless such testing is not appropriate for the population (e.g. terminally ill patients) or product to be studied. The genetic toxicology tests should include a bacterial mutation assay using all five tester strains with and without metabolic activation[18] as well as a test for chromosomal damage either in vitro (cytogenetics assay or mouse lymphoma thymidine kinase gene mutation assay) or in vivo. The in vivo test can be a micronucleus assay performed in conjunction with the repeated dose toxicity study in the rodent species. The high dose in this case should be a maximally tolerated or limit dose.

The results from the preclinical program can be used to select starting and maximum doses for the clinical trials. The starting dose is anticipated to be no greater than 1/50 of the NOAEL from the 2-week toxicology study in the sensitive species on a $mg/m^2$ basis. The maximum clinical dose would be the lowest of the following:

- ¼ of the 2-week rodent NOAEL on a $mg/m^2$ basis
- Up to ½ of the AUC at the NOAEL in the 2-week rodent study, or the AUC in the dog at the rat NOAEL, whichever is lower
- The dose that produces a pharmacologic and/or pharmacodynamic response or at which target modulation is observed in the clinical trial
- Observation of an adverse clinical response

Escalation from the proposed maximal clinical dose should only be performed after consultation with and concurrence of the FDA.

It is recognized that the studies described above are most appropriate for chemical drugs. Other animal models (e.g. nonhuman primates) may be more appropriate for biologics, and some tests may be inappropriate (e.g. genetic toxicology testing) for proteins.

*3. Clinical studies of MOAs related to efficacy*

A third example involves clinical studies intended to evaluate mechanisms of action (MOAs). To support this approach, the FDA will accept alternative, or modified, pharmacologic and toxicological studies to select clinical starting doses and dose escalation schemes. For example, short-term, modified toxicity or safety studies in two animal species based on a dosing strategy to achieve a clinical pharmacodynamic endpoint can in some instances serve as the basis for selecting the safe clinical starting dose for a new candidate drug. These animal studies would incorporate endpoints that are mechanistically based on the pharmacology of the new chemical entity and thought to be important to clinical effectiveness. For example, if the degree of saturation of a receptor or the inhibition of an enzyme were considered possibly related to effectiveness, this parameter would be characterized and determined in the animal study and then used as an endpoint in a subsequent clinical investigation. The dose and dosing regimen determined in the animal study would be extrapolated for use in the clinical investigation. In some cases, a single species could be used if it were established as the most relevant species based on scientific evidence using the specific candidate intended for the clinical investigation.

[18] *For* details see guidance for industry *S2A: Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* and *S2B: Genotoxicity: A Standard Battery for Genotoxicity Testing for Pharmaceuticals*.

Although the production of frank toxicity is not the primary intended goal of the nonclinical study, relevant informative endpoints (e.g., hematology and histopathology) selected as important for clinical safety evaluation should be investigated. For example, an antibody that binds with a high degree of selectivity to a tumor-associated antigen could be studied in accordance with this third category. The mechanism of action of antibody-based products is generally associated with their binding properties and the effect on functions associated with immunoglobulins. Pharmacology and toxicology studies provide information about the selection of doses used in clinical studies through evidence of both a safe upper and potentially efficacious lower limit of exposure. These doses might be consistent with target plasma levels of the drug based on animal models of disease. The upper safe levels could be established in animal studies that show a lack of toxicity at these levels.

### D. GLP Compliance

It is expected that all preclinical safety studies supporting the safety of an exploratory IND application will be performed in a manner consistent with good laboratory practices (GLP) (21 CFR Part 58). The GLP provisions apply to a broad variety of studies, test articles, and test systems. Sponsors are encouraged to discuss any need for an exemption from GLP provisions with the FDA prior to conducting safety related studies, for example, during a pre-IND meeting. Sponsors must justify any nonconformance with GLP provisions (21 CFR 312.23(a)(8)(iii)).

## IV. CONCLUSION

Existing regulations allow a great deal of flexibility in the amount of data that needs to be submitted with any IND application, depending on the goals of an investigation, the specific human testing being proposed, and the expected risks. Sponsors have not taken full advantage of that flexibility, and limited, early phase 1 studies, such as those described in this guidance, are often supported by a more extensive preclinical database than is needed for those studies alone.

The common theme throughout this guidance is that, depending on the study, the preclinical testing programs for exploratory IND studies can be less extensive than for traditional IND studies. This is because for the approaches discussed in this guidance, which involve administering sub-pharmacologic doses of a candidate product or products, the potential risks to human subjects are less than for a traditional phase 1 study.

The Agency is undertaking a number of efforts to reduce the time spent in early drug development on products that are unlikely to succeed. This guidance describes some exploratory approaches that are consistent with regulatory requirements, but that will enable sponsors to move ahead more efficiently with the development of promising candidate products while maintaining needed human subject protections.

## ATTACHMENT

A Preclinical Toxicology Testing Strategy for Exploratory INDs Designed To Administer Pharmacologically Active Doses