Guidance for Industry

Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products

Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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GUIDANCE FOR INDUSTRY[1]

CONTENT AND FORMAT OF INVESTIGATIONAL NEW DRUG APPLICATIONS (INDs) FOR PHASE 1 STUDIES OF DRUGS, INCLUDING WELL-CHARACTERIZED, THERAPEUTIC, BIOTECHNOLOGY-DERIVED PRODUCTS

I. INTRODUCTION

With FDA's recent successes in meeting the Prescription Drug User Fee Act of 1992 (PDUFA) review action performance goals, and the resulting significant declines in mean and median time from submission of a marketing application to approval for marketing, attention has turned to increasing the efficiency of other components of the drug development process without sacrificing the long-standing safety and efficacy standards Americans expect their drug products to meet. One part of IND regulation of particular interest - under active discussion for more than two years and the subject of various degrees of attention since the McMahon Committee - is the regulation of the initial testing of drugs in humans (*i.e.,* Phase 1 trials).

This guidance clarifies requirements for data and data presentation in 21 CFR 312.22 and 312.23 related to the initial entry into human studies in the United States of an investigational drug, including well-characterized, therapeutic, biotechnology-derived products[2]. Present regulations allow a great deal of

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[1]This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. Although this guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the industry, it does represent the agency's current thinking on data requirement issues related to the initial entry of an unapproved drug into human studies in the United States. For additional copies of this guidance, contact the Consumer Affairs Branch (formerly the Executive Secretariat Staff), HFD-210, CDER, FDA, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-594-1012) or the Congressional and Consumer Affairs Branch (HFM-12), CBER, FDA, 1401 Rockville Pike (STE 200N), Rockville, MD 20852-1448 (Phone: 301-594-1800 or 800-835-4709). An electronic version of this guidance is also available via Internet by connecting to the CDER file transfer protocol (FTP) server (CDVS2.CDER.FDA.GOV).

[2]As used throughout this guidance, the term "drugs" includes well-characterized, therapeutic, biotechnology-derived products.

flexibility in the amount and depth of various data to be submitted in an IND depending in large part on the phase of investigation and the specific human testing being proposed. In some cases, the extent of that flexibility has not been appreciated. FDA believes clarifications of many of these requirements will help expedite entry of new drugs into clinical testing by increasing transparency and reducing ambiguity and inconsistencies, and by reducing the amount of information submitted, while providing FDA with the data it needs to assess the safety of the proposed Phase 1 study. If the guidance specified in this document is followed, IND submissions for Phase 1 studies should usually not be larger than two to three, three inch, 3-ring binders ("jackets").

The most significant clarifications are: 1) the explicit willingness to accept an integrated summary report of toxicology findings based upon the unaudited draft toxicologic reports of completed animal studies as initial support for human studies, and 2) specific manufacturing data appropriate for a Phase 1 investigation. For products not covered by this Guidance, other FDA guidance documents should be consulted. In addition, the Center responsible for the product may be contacted for guidance.

Because of the manufacturing and toxicologic differences between well-characterized, therapeutic, biotechnology-derived products and other biologic products, this Guidance only applies to drugs and well-characterized, therapeutic, biotechnology-derived products. For products not covered by this Guidance, the Center responsible for the product should be contacted for guidance.

This guidance applies equally to both commercial and individual investigator sponsored INDs.

II. CURRENT REQUIREMENTS AND PRACTICES

Under current regulations, any use in the United States of a drug product not previously authorized for marketing in the United States first requires submission of an IND to the FDA. Current regulations at 21 CFR 312.22 and 312.23 contain the general principles underlying the IND submission and the general requirements for an IND's content and format.

III. CLARIFICATIONS OF PRESENT IND REGULATIONS

An IND submission for Phase 1 studies is required by regulation to contain the sections enumerated below. Clarifications are described when appropriate beneath each section heading.

A. Cover Sheet (FDA Form-1571) [21 CFR 312.23(a)(1)]:

No clarifications.

B. Table of Contents [21 CFR 312.23(a)(2)]:

No clarifications.

C. Introductory Statement and General Investigational Plan [21 CFR 312.23(a)(3)]:

Regulations repeatedly describe this section as brief. Ordinarily, two to three pages should suffice. The information requested here is intended to place the developmental plan for the drug into perspective and to help FDA anticipate sponsor needs. Often a sponsor in the first human studies is simply attempting to determine early pharmacokinetic and perhaps early pharmacodynamic properties of the drug. Detailed developmental plans are contingent on the outcomes of such studies. In that case, sponsors should simply state this in this section and not attempt to develop and write detailed developmental plans that will, in all likelihood, change considerably should the product proceed to further development.

D. Investigator's Brochure [21 CFR 312.23(a)(5)]:

Under the auspices of the International Conference on Harmonization (ICH), a document that provides general guidance on the Investigator's Brochure has been developed and will soon be published in the *Federal Register* (*Good Clinical Practice: Guideline for the Investigator's Brochure*). Sponsors are referred to this document for further information on recommended elements of an Investigator's Brochure.

E. Protocols [21 CFR 312.23(a)(6)]:

The regulation requires submission of a copy of the protocol for the conduct of each proposed clinical trial. Sponsors are reminded that the regulations were changed in 1987 specifically to allow Phase 1 study protocols to be less detailed and more flexible than protocols for Phase 2 or 3 studies. This change recognized that these protocols are part of an early learning process and should be adaptable as information is obtained, and that the principal concern at this stage of development is that the study be conducted safely. The regulations state that Phase 1 protocols should be directed primarily at providing **an outline** of the

investigation: an estimate of the number of subjects to be included; a description of safety exclusions; and a description of the dosing plan, including duration, dose, or method to be used in determining dose. In addition, such protocols should specify in detail **only** those elements of the study that are critical to subject safety, such as: 1) necessary monitoring of vital signs and blood chemistries and 2) toxicity-based stopping or dose adjustment rules. In addition, the regulations state that modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA **only** in the IND annual report.

F. Chemistry, Manufacturing, and Control Information [21 CFR 312.23(a)(7)]:

The regulations at 312.23(a)(7)(i) emphasize the graded nature of manufacturing and controls information. Although in each phase of the investigation sufficient information should be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly very limited.

It is recognized that modifications to the method of preparation of the new drug substance and dosage form, and even changes in the dosage form itself, are likely as the investigation progresses. The emphasis in an initial Phase 1 CMC submission should, therefore, generally be placed on providing information that will allow evaluation of the safety of subjects in the proposed study. The identification of a safety concern or insufficient data to make an evaluation of safety is the only basis for a clinical hold based on the CMC section.

Reasons for concern may include, for example: 1) a product made with unknown or impure components; 2) a product possessing chemical structures of known or highly likely toxicity; 3) a product that cannot remain chemically stable throughout the testing program proposed; or 4) a product with an impurity profile indicative of a potential health hazard or an impurity profile insufficiently defined to assess a potential health

hazard; or 5) a poorly characterized master or working cell bank.

In addition, for pre-clinical studies to be useful in assuring the safety of human studies, sponsors should be able to relate the drug product being proposed for use in a clinical study to the drug product used in the animal toxicology studies that support the safety of the proposed human study.

The information discussed in the following numbered paragraphs should usually suffice for a meaningful review of the manufacturing procedures for drug products used in Phase 1 clinical studies. Additional information should ordinarily be submitted for review of the larger-scale manufacturing procedures used to produce drug products for Phase 2 or Phase 3 clinical trials or as part of the manufacturing section of a marketing application. Any questions sponsors have about potential large scale IND clinical trials or potential marketing application manufacturing requirements or specifications should be directed to the appropriate division in the CDER Office of New Drug Chemistry, or the appropriate CBER division with responsibility for the product, for clarification and discussion. As clinical development of a drug product proceeds, sponsors should discuss the manufacturing data that will be needed to support the safe use of their products in Phase 2 and 3 trials with the appropriate division in the CDER Office of New Drug Chemistry, or the appropriate CBER division with responsibility for the product.

1. Chemistry and Manufacturing Introduction:

At the beginning of this section, the sponsor should state whether it believes: 1) the chemistry of either the drug substance or the drug product, or 2) the manufacturing of either the drug substance or the drug product, presents any signals of potential human risk. If so, these signals of potential risks should be discussed, and the steps proposed to monitor for such risk(s) should be described, or the reason(s) why the signal(s) should be dismissed should be discussed.

In addition, sponsors should describe any chemistry and manufacturing differences between the drug product proposed for clinical use and the drug product used in the animal toxicology trials that formed the basis for the sponsor's conclusion that it was safe to proceed with the proposed clinical study. How these differences might affect the safety profile of the drug product should be discussed. If there are no differences in the products, that should be stated.

2. Drug Substance [312.23 (a)(7)(iv)(a)]:

Sponsors are reminded that, under present regulations, references to the current edition of the USP-NF may be used to satisfy some of the requirements, when applicable.

Information on the drug substance should be submitted in a summary report containing the following items.

a. A description of the drug substance, including its physical, chemical, or biological characteristics:

A brief description of the drug substance and some evidence to support its proposed chemical structure should be submitted. It is understood that the amount of structure information will be limited in the early stage of drug development.

b. The name and address of its manufacturer:

The full street address of the manufacturer of the clinical trial drug substance should be submitted.

c. The general method of preparation of the drug substance:

A brief description of the manufacturing process, including a list of the reagents, solvents, and catalysts used, should be submitted. A detailed flow diagram is suggested as the usual, most effective, presentation of this information. More information may be needed to assess the safety of biotechnology-derived drugs or drugs extracted from human or animal sources.

d. The acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance:

A brief description of the test methods used should be submitted. Proposed acceptable limits supported by simple analytical data, (*e.g.*, IR spectrum to prove the identity, and HPLC chromatograms to support the purity level and impurities profile) of the clinical trials material should be

provided. Submission of a copy of the certificate of analysis is also suggested. The specific methods will depend on the source and type of drug substance (*e.g.*, animal source, plant extract, radiopharmaceutic, other biotechnology-derived products). Validation data and established specifications ordinarily need not be submitted at the initial stage of drug development. However, for some well-characterized, therapeutic biotechnology-derived products, preliminary specifications and additional validation data may be needed in certain circumstances to ensure safety in Phase 1.

e. Information to support the stability of the drug substance during the toxicologic studies and the proposed clinical study(ies):

A brief description of the stability study and the test methods used to monitor the stability of the drug substance should be submitted. Preliminary tabular data based on representative material may be submitted. Neither detailed stability data nor the stability protocol should be submitted.

3. Drug Product [21 CFR 312.23 (a)(7)(iv)(b)]:

Sponsors are reminded that, under present regulations, references to the current edition of the USP-NF may be used to satisfy some of these requirements, when applicable.

Information on the drug product should be submitted in a summary report containing the following items:

a. A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear, but which are used in the manufacturing process:

A list of usually no more than one or two pages of written information should be submitted. The quality (*e.g.*, NF, ACS) of the inactive ingredients should be cited. For novel excipients, additional manufacturing information may be

necessary.

b. Where applicable, the quantitative composition of the investigational new drug product, including any reasonable variations that may be expected during the investigational stage:

A brief summary of the composition of the investigational new drug product should be submitted. In most cases, information on component ranges is not necessary.

c. The name and address of the drug product manufacturer:

The full street address(es) of the manufacturer(s) of the clinical trial drug product should be submitted.

d. A brief, general description of the method of manufacturing and packaging procedures as appropriate for the product:

A diagrammatic presentation and a brief written description of the manufacturing process should be submitted, including sterilization process for sterile products. Flow diagrams are suggested as the usual, most effective, presentations of this information.

e. The acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product:

A brief description of the proposed acceptable limits and the test methods used should be submitted. Tests that should be submitted will vary according to the dosage form. For example, for sterile products, sterility and non-pyrogenicity tests should be submitted. Submission of a copy of the certificate of analysis of the clinical batch is also suggested. Validation data and established specifications need not be submitted at the initial stage of drug development. For well-characterized, therapeutic, biotechnology-derived products, adeaute assessment of bioactivity and preliminary specifications should be available.

f. Information to support the stability of the drug substance during the toxicologic studies and the proposed clinical study(ies):

A brief description of the stability study and the test methods used to monitor the stability of the drug product packaged in the proposed container/closure system and storage conditions should be submitted. Preliminary tabular data based on representative material may be submitted. Neither detailed stability data nor the stability protocol should be submitted.

4. A brief general description of the composition, manufacture, and control of any placebo to be used in the proposed clinical trial(s) [21 CFR 312.23(a)(7)(iv)(c)]:

Diagrammatic, tabular, and brief written information should be submitted.

5. A copy of all labels and labeling to be provided to each investigator [21 CFR 312.23(a)(7)(iv)(d)]:

A mock-up or printed representation of the proposed labeling that will be provided to investigator(s) in the proposed clinical trial should be submitted. Investigational labels must carry a "caution" statement as required by 21 CFR 312.6(a). That statement reads: "Caution: New Drug - Limited by Federal (or United States) law to investigational use."

6. A claim for categorical exclusion from or submission of an environmental assessment [21 CFR 312.23(a)(7)(iv)(e)]:

FDA believes the great majority of products should qualify for a categorical exclusion. Sponsors who believe their investigational product meets the exclusion categories under 21 CFR 25.24 should submit a statement certifying that their product meets the exclusion requirements and requesting a categorical exclusion on that basis. (For INDs submitted to CDER, see *Guidance for Industry for the Submission of Environmental Assessments for Human Drug Applications and Supplements*, November, 1995.)

G. Pharmacology and Toxicology Information [21 CFR 312.23(a)(8)]:

[The following pharmacology and toxicology guidance is applicable to all phases of IND development of products covered by this guidance.]

1. Pharmacology and Drug Distribution [21 CFR 312.23(a)(8)(i)]:

This section should contain, if known: 1) a description of the pharmacologic effects and mechanism(s) of actions of the drug in animals, and 2) information on the absorption, distribution, metabolism, and excretions of the drug. The regulations do not further describe the presentation of these data, in contrast to the more detailed description of how to submit toxicologic data. A summary report, without individual animal records or individual study results, usually suffices. In most circumstances, five pages or less should suffice for this summary. If this information is not known, it should simply be so stated.

To the extent that such studies may be important to address safety issues, or to assist in evaluation of toxicology data, they may be necessary; however, lack of this potential effectiveness information should not generally be a reason for a Phase 1 IND to be placed on clinical hold.

2. Toxicology: Integrated Summary [21 CFR 312.23(a)(8)(ii)(a)]

Present regulations require an integrated summary of the toxicologic effects of the drug in animals and *in vitro*. The particular studies needed depend on the nature of the drug and the phase of human investigation. When species specificity, immunogenicity, or other considerations appear to make many or all toxicological models irrelevant, sponsors are encouraged to contact the agency to discuss toxicological testing.

The regulations are not specific as to the nature of the report of toxicology data needed in an IND submission and the nature of the study reports upon which the report submitted to the IND is based. The regulations are silent on whether the submitted material should be based on: 1) "final fully quality-assured" individual study reports, or 2) earlier, unaudited draft toxicologic reports of the completed study(ies). Most sponsors have concluded that a

submission based on final fully quality-assured individual study reports is required, and a substantial delay in submission of an IND for several months is often encountered to complete such final fully quality-assured individual reports from the time the unaudited draft toxicologic reports of the completed studies are prepared.

Moreover, although the regulation does not specifically require individual toxicology study reports to be submitted, referring only to an integrated summary of the toxicologic findings, the requirement at 21 CFR 312.23(a)(8)(ii)(b) for a full tabulation of data from each study suitable for detailed review has led most sponsors to provide detailed reports of each study.

Although the GLP and quality assurance processes and principles are critical for the maintenance of a toxicology study system that is valid and credible, it is unusual, as far as FDA is aware, for findings in the unaudited draft toxicologic report of the completed studies to change during the production of the "final," quality-assured individual study reports in ways important to determining whether use in humans is safe.

Therefore, if final, fully quality-assured individual study reports are not available at the time of IND submission, an integrated summary report of toxicologic findings based on the unaudited draft toxicologic reports of the completed animal studies may be submitted. This integrated summary report should represent the sponsor's evaluation of the animal studies that formed the basis for the sponsor's decision that the proposed human studies are safe. It is expected that the unaudited draft reports that formed the basis of this decision might undergo minor modifications during final review and quality assurance auditing. Full toxicology department individual study reports should be available to FDA, upon request, and individual study reports should be available to FDA, upon request, as final, fully quality-assured documents within 120 days of the start of the human study for which the animal study formed part of the safety conclusion basis. These final reports should contain in the introduction any changes from those reported in the integrated summary. If there are no changes, that should be so stated clearly at the beginning of the final, fully quality-assured report.

If the integrated summary is based upon unaudited draft reports,

sponsors should submit an update to their integrated summary by 120 days after the start of the human study(ies) identifying any differences found in the preparation of the final fully quality-assured study reports and the information submitted in the initial integrated summary. If there were no differences found, that should be stated in the integrated summary update.

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In addition, any new finding discovered during the preparation of the final, fully quality-assured individual study reports that could affect subject safety must be reported to FDA under 21 CFR 312.32.

Usually, 10 to 15 pages of text with additional tables (as needed) should suffice for the integrated summary. It should represent the sponsor's perspective on the completed animal studies at the time the sponsor decided human trials were appropriate. Use of visual data displays (*e.g.*, box plots, stem and leaf displays, histograms or distributions of lab results over time) will facilitate description of the findings of these trials.

The summary document should be accurate contemporaneously with the IND submission (*i.e.,* it should be updated so that if new information or findings from the completed animal studies have become known since the sponsor's decision that the proposed human study is safe, such new information should also be included in the submitted summary).

The integrated summary of the toxicologic findings of the completed animal studies to support the safety of the proposed human investigation should ordinarily contain the following information:

a. A brief description of the design of the trials and any deviations from the design in the conduct of the trials. In addition, the dates of the performance of the trials should be included. Reference to the study protocol and protocol amendments may suffice for some of this information.

b. A systematic presentation of the findings from the animal toxicology and toxicokinetic studies. Those findings that an informed and experienced expert would reasonably consider as possible signals of human risk should be highlighted. The format of this part of the summary may be

approached from a "systems review" perspective: (*e.g.*, CNS, cardiovascular, pulmonary, gastrointestinal, renal, hepatic, genitourinary, hematopoietic and immunologic, and dermal). If a product's effects on a particular body system have not been assessed, that should be so noted. If any well-documented toxicological "signal" is not considered evidence of human risk, the reason should be given. In addition, the sponsor should note whether these findings are discussed in the investigator's brochure.

c. Identification and qualifications of the individual(s) who evaluated the animal safety data and concluded that it is reasonably safe to begin the proposed human study. This person(s) should sign the summary attesting that the summary accurately reflects the animal toxicology data from the completed studies.

d. A statement of where the animal studies were conducted and where the records of the studies are available for inspection, should an inspection occur.

e. As required under 21 CFR 312.23(a)(8)(iii), a declaration that each study subject to good laboratory practices (GLP) regulations was performed in full compliance with GLPs or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance and the sponsor's view on how such non-compliance might affect the interpretations of the findings.

NOTE: The information described in paragraphs "c", "d", and "e" may be supplied as part of the integrated summary or as part of the full data tabulations described below.

3. Toxicology - Full Data Tabulation [21 CFR 312.23(a)(8)(ii)(b)]:

The sponsor should submit, for each animal toxicology study that is intended to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review. This should consist of line listings of the individual data points, including laboratory data points, for each animal in these trials along with summary tabulations of these data points. To allow interpretation of the line listings, accompanying the line listings

should be either: 1) a brief (usually a few pages) description (*i.e.*, a technical report or abstract including a methods description section) of the study or 2) a copy of the study protocol and amendments.

4. Toxicology - GLP Certification [21 CFR 312.23(a)(8)(iii)]:

See section III.G.2.e. above.

5. Monitoring of Effects of these Clarifications:

At the end of the first two to three years of this new procedure, FDA will assemble and examine the instances in which the early and later animal study individual reports differed to determine if such differences made a material difference in the safe conduct of human trials. Depending on the outcomes, the acceptability of this approach to reporting toxicology studies to INDs may be re-examined.

H. Previous Human Experience with the Investigational Drug [21 CFR 312.23(a)(9)]:

Present regulations require this information only if there has been previous human experience with the investigational drug. If there has been no previous human experience, the submission should so state.

When there has been previous human experience, such experience may be presented in an integrated summary report. Individual study reports should not be routinely submitted.

I. 21 CFR 312.23(a)(10), (11) and (b), (c), (d), and (e) :

No clarifications.

IV. REFERENCES

A. Food and Drug Administration, Center for Drug Evaluation and Research, "IND Process and Review Procedures" (MAPP xxxx.x), *Manual of Policies and Procedures*, November, 1995.

B. International Conference on Harmonization: *Good Clinical Practice: Guideline for the Investigator's Brochure*.

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