Draft - Not for Implementation

Guidance for Industry

Submission of Abbreviated Reports and Synopses in Support of Marketing Applications

DRAFT GUIDANCE

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Copies of this draft guidance are available from the Office of Training and Communications, Division of Communications Management, Drug Information Branch, HFD-210, 5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573 or from the Internet at http://www.fda.gov/cder/guidance/index.htm.

Copies also are available from the Office of Communication, Training and Manufacturers Assistance, HFM-40, CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448, or from the Internet at http://www.fda.gov/cber/guidelines.htm. Copies also may be obtained by fax from 1-888-CBERFAX or 301-827-3844 or by mail from the Voice Information System at 800-835-4709 or 301-827-1800.

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U.S. Department of Health and Human Services
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TABLE OF CONTENTS

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Guidance for Industry[1]
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I. INTRODUCTION

This document provides guidance to applicants on submitting abbreviated reports and synopses in lieu of full reports for certain clinical studies, both in marketing applications for new drug and biological products and in supplements to approved applications. This guidance is intended to meet the requirements of Section 118 of the Food and Drug Administration Modernization Act of 1997 (Modernization Act), which directs FDA to issue guidance on when abbreviated study reports may be submitted in new drug applications (NDAs) and biologics license applications (BLAs) in lieu of full reports.

This guidance focuses on the circumstances when full study reports, abbreviated reports, and synopses can be used to submit data concerning the effectiveness of new drugs and biological products. Generally, full reports on safety are required. However, in some instances, the safety data in a particular study may not be germane to the proposed use and a complete discussion of safety may be unnecessary. The guidance also describes the recommended formats for abbreviated reports and synopses. Applicants are urged to discuss the planned report formats for a specific application with the appropriate review division prior to submission.

II. BACKGROUND

Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act provides that full reports of the investigations to demonstrate a product's safety and effectiveness be submitted in an NDA. Similarly, for BLAs FDA often requires that a manufacturer submit full reports to demonstrate that the biological product is safe, pure, and potent. The NDA regulations at 21 CFR 314.50,

[1]This draft 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 (FDA). This draft guidance document represents the Agency's current thinking on the submission of full study reports, abbreviated reports, and synopses of information related to effectiveness for new drugs and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

which define what must be submitted in an application, do not explicitly define a full report, but require, among other things, submission of a "description and analysis of each controlled clinical study pertinent to a proposed use of the drug" and of "any other data or information relevant to an evaluation of the safety and effectiveness of the drug product" [21 CFR 314.50(d)(5)].

In 1988 , FDA issued *Guidelines for the Format and Content of the Clinical and Statistical Sections of New Drug Applications* (*Clin/Stat Guideline*), which called for full study reports only for studies that contributed effectiveness data as well as safety information. For other studies, applicants were advised to submit abbreviated reports of the effectiveness results. In 1996, the International Conference on Harmonisation of the Technical Requirements for Registration of Pharmaceuticals (ICH) *Guidelines for the Structure and Content of Clinical Study Reports* (ICH E3), provided an updated description of the contents of a full study report and specific provisions for submission of less-than-full study reports.

In the past, applicants have not used the provisions to submit less-than-full study reports contained in both the *Clin/Stat Guideline* and ICH E3 as much as they could have because of difficulties deciding when a full study report is required by the reviewing body. For example, clinical drug and biological product development programs often include numerous clinical studies and resulting data that are not intended to contribute to the evaluation of the effectiveness of a product for a particular use and are not needed to support information included in labeling. Accordingly, such studies may be submitted as abbreviated reports or synopses, and this guidance is intended to facilitate their submission.

This guidance addresses studies submitted in the following sections of an NDA or BLA:

- human pharmacokinetics and bioavailability [21 CFR 314.50(d)(3) and 601.2, section 6 of FDA 356h]
- clinical data (including clinical pharmacology) [21 CFR 314.50(d)(5) and 601.2, section 8 of FDA 356h]
- statistical [21 CFR 314.50(d)(6) and 601.2, section 10 of FDA 356h]

Clinical pharmacology studies are defined in the human pharmacokinetics, bioavailability, and clinical pharmacology section of this guidance to include pharmacokinetics (i.e., absorption, distribution, metabolism, and excretion — ADME) and/or pharmacodynamic studies (i.e., dose and/or concentration/range and dose and/or concentration/response), including those performed in special populations, drug-drug interaction studies, and population pharmacokinetics and/or pharmacodynamic studies (PK/PD screens). In addition, clinical pharmacology studies are defined to include *mass balance studies, other human pharmacology studies, studies in human tissues, organs, cell cultures,* and *cellular and/or subcellular fractions*, and any *associated assay validation studies*. As defined in this guidance, biopharmaceutics studies include *bioavailability, bioequivalence, food effect studies, permeability studies, in vitro dissolution and solubility*

studies, and *associated assay validation studies*.

III. SUBMISSION OF STUDY REPORTS

The information on clinical investigations required under 21 CFR 314.50 should be submitted in one of three formats: (1) full study reports, (2) abbreviated reports, or (3) synopses.

Full study reports (i.e., the complete ICH E3 report) should be submitted for all clinical and human pharmacology investigations that contribute to the evaluation of effectiveness for the proposed indication, or that otherwise support information included in labeling.

During the development of a product, studies may be conducted that ultimately do not contribute to the evaluation of the effectiveness of a product for a specific indication. As discussed more fully below, such studies should be submitted as either abbreviated reports or synopses.

Abbreviated reports should be submitted for studies that are not intended to contribute to the evaluation of product effectiveness or provide definitive information on clinical pharmacology, but about which the reviewer needs sufficient information to determine that the study results do not cast doubt on the effectiveness claims or the description of the clinical pharmacology. Abbreviated reports should contain all the *safety* information included in a full report.

Synopses should be submitted for studies that are not relevant to the evaluation of product effectiveness or clinical pharmacology, but that provide information the reviewer needs to evaluate the safety data from the study. Complete safety information from a study submitted in synopsis format should be included in the Integrated Summary of Safety (ISS) [21 CFR 314.50(d)(5)(vi)(a)] for drug products and for biological products where an ISS is included in the application. For biological product applications not containing an ISS, the safety information for studies submitted in synopsis format should be appended to the synopsis.

Clinical drug development programs vary widely in the number of studies performed and the number of patients studied. Development programs with many studies and many exposed patients are likely to compile a substantial database from controlled trials, as well as from less relevant trials that should be submitted in a less-than-full format. In contrast, applications for products that have undergone rapid development programs (typically for serious or life-threatening diseases without adequate therapy), or products intended for orphan indications, may compile only a small total database. In such cases, detailed evaluation of all available information may be critical to assessing the product's safety and effectiveness. Therefore, applicants should plan to file full study reports for products that are the subject of very limited development programs (defined for the purposes of this guidance as fewer than six clinical trials, including dose-comparison trials, designed to determine efficacy). However, even in small clinical development programs, it is

possible that certain studies need not be submitted as full reports, if there is agreement in advance with the relevant reviewing division on studies that may be submitted as abbreviated reports or synopses.

In general, because it may be difficult to distinguish among studies that require full reports, abbreviated reports, or synopses, applicants should confer with the relevant reviewing division prior to deciding the format in which studies will be reported. The goals of a consultation would be to limit study reporting in applications to that which is essential to document the evidence of effectiveness for Agency review, and to minimize the need for the Agency to request full study reports for studies originally reported in abbreviated or synopsis format (see section VI).

A. Clinical Efficacy and Safety Studies

1. Studies for which full reports should be submitted

Full study reports (i.e., the complete ICH E3) should ordinarily be submitted for all studies from clinical investigations of drugs or biological products that are the subject of very limited clinical development programs (i.e., programs with fewer than six clinical trials from any phase of drug development designed to determine effectiveness, including dose-comparison trials).

In addition, full study reports should be submitted for clinical effectiveness studies that (a) evaluate a dose, regimen, patient population, and indication for which marketing approval is sought, and (b) are capable by design, conduct, and enrollment of assessing the effectiveness of the product. Full study reports are expected for these studies whether or not they demonstrate a treatment effect. Examples include:

- Studies providing the basis for dose recommendations (e.g., dose-comparison studies).
- Controlled studies identified by the applicant as contributing directly to substantial evidence of effectiveness.
- Controlled studies that support an intended comparative claim.
- Controlled studies considered supportive of effectiveness (e.g., studies believed to show a favorable trend, possible effect in a subgroup).
- Controlled studies of different indications (stages of disease, different study populations) or dosage forms or regimens if they are intended to provide support for approval.

- Controlled studies evaluating effectiveness for the indication that failed to show an effect.

2. Studies for which abbreviated reports should be submitted

Abbreviated reports should be submitted for studies that do not fall under A.1., and that meet the following conditions: (1) The studies are not intended to contribute to the evaluation of product effectiveness, but (2) the reviewer needs sufficient information about the studies to determine that their results do not cast doubt on the effectiveness claims for the product. Abbreviated reports should also be submitted for studies that do not fall under A.1., but that contribute significantly to the safety database. Abbreviated reports should contain a full safety report.

Examples of studies that should be submitted as abbreviated reports include:

- Studies with active controls that do not provide the primary or substantiating evidence of effectiveness (e.g., active-controlled equivalence trials from clinical development programs in which the primary evidence of effectiveness is contributed by placebo-controlled, dose-controlled, or other superiority designs). Active-controlled trials in which differences were observed or that support a claim in labeling should be submitted as full study reports.

- Studies of related indications for which marketing approval is not being sought (unless they are intended to provide significant substantiating evidence of effectiveness for the indications being sought).

- Studies not designed as efficacy studies or designed as efficacy studies for different indications that contribute significant information about product safety (e.g., large, randomized or nonrandomized trials where enrollment approached or exceeded the size of the efficacy trials, or expanded access studies that collected information related to efficacy).

- Studies of doses or dosage forms not intended for marketing (unless they are intended to provide significant substantiating evidence of effectiveness)**.**

- Controlled (i.e., hypothesis testing) safety studies may be submitted as abbreviated reports; however, as for all studies, adequate detail on study design and conduct to permit complete analysis of safety should be provided.

In some cases, with agreement from the relevant reviewing division, applicants may file

negative studies (studies failing to show a treatment effect) as abbreviated reports if the efficacy trials proposed to be filed as full reports are judged adequate for evaluation of effectiveness. In such cases, the format for display of the efficacy data (see Section IV. A) should be agreed upon in advance.

3. Studies for which synopses should be submitted

Some studies are generally only examined in sufficient depth to assess if they cast doubt on the safety of the product for the proposed indication. For these studies, complete safety information should be included in the ISS or, for biological products not containing an ISS, the safety information should be appended to the synopsis. Examples of studies that should be submitted as synopses include:

- Studies of unrelated indications for which marketing approval is not being sought (unless they form a significant portion of the safety database, in which case they should be submitted as abbreviated reports).

- Studies evaluating routes of administration for which marketing approval is not being sought.

- Incomplete studies, defined for the purpose of this guidance as enrolling fewer than one-third of intended patients, unless stopped for safety reasons or for futility (inability to show efficacy). Those studies stopped for safety reasons or due to futility should be submitted as abbreviated reports.

- Uncontrolled studies not specifically identified as needing abbreviated or full study reports.

- Early safety-tolerance studies in Phase 1, but not specific toxicity studies (e.g., dermatotoxicity studies), which ordinarily should be submitted as full reports.

B. Human Pharmacokinetics, Bioavailability, and Clinical Pharmacology Studies

Sponsors of products with very limited development programs should consult the relevant review division prior to submitting less-than-full reports for studies in this section.

1. Studies for which full reports should be submitted:

- Clinical pharmacology and biopharmaceutics studies that support labeling statements.

- The most relevant in a series of similar studies (e.g., for a series of three food-drug interaction studies, only the most relevant study would be submitted as a full report). For the purposes of this guidance, *most relevant* means the study with the best design, power, dose, or study population to address the study question and the intended dose, indication, and patient population. When studies in a series are not in agreement, all studies of that type should be submitted as full reports.

- Dose ranging studies to determine the dose(s) for phase 2-3 studies.

- Bioavailability and bioequivalence studies that compare performance of the formulation or dosage form used in clinical trials to that intended for marketing.

- One representative assay validation study for each analytical method at each analytical site.

2. Studies for which abbreviated reports should be submitted:

- Less relevant studies in a series of similar studies (see above).

- Bioavailability/bioequivalence studies not assessing performance of material used in clinical trials relative to dosage forms intended for marketing.

3. Studies for which synopses should be submitted:

- Studies that have been shown to have defects in design, conduct, data handling or analysis that render them incapable of supporting a useful and/or relevant conclusion.

- Studies evaluating dosage forms no longer under development.

- Discontinued studies.

- Studies from abandoned indications.

IV. FORMAT OF AN ABBREVIATED CLINICAL REPORT

A. Clinical Efficacy Studies

An abbreviated report should contain a full report of information related to safety and enough information to allow the reviewers to fully assess whether the efficacy results, if any, cast doubt

on the effectiveness of the product for the proposed indication. As described below, the abbreviated study report should contain only selected sections of ICH E3. An abbreviated report should include all safety information included in a full report, whereas efficacy information should be concise and not as comprehensive as in a full report.

The following sections should be included in an abbreviated study report (the numbered sections are described in ICH E3):

- Section 1 - Title page
- Section 2 - Synopsis
- Section 3 - Table of contents for the individual clinical study report
- Section 4 - List of abbreviations and definitions of terms
- Section 9.1 - Overall study and design and plan: description
- Section 9.8 - Changes in the conduct of the study or planned analyses
- Section 10.1 - Disposition of patients
- Section 12 - Safety evaluation
- Section 13 - Discussion and overall conclusions
- Section 14 - Tables, figures and graphs referred to but not included in the text
- Section 16.1.1 - Protocol and protocol amendments
- Section 16.1.2 - Sample case report forms (unique pages only)
- Section 16.3.1 - Case report forms for deaths, other serious adverse events and withdrawals for adverse events (submit under item 12 - FDA form 356h)
- Section 16.4 - Individual patient data listings (for safety data)
- A summary of the efficacy evaluation (suggested to be primarily in table form). The summary should contain enough information for the reviewer to determine whether the study results are germane to the overall evaluation of effectiveness and to use in review of the integrated analysis of effectiveness, if necessary (including means, confidence, intervals, p-values, standard errors, etc.) Section 11.4.1 of ICH E3 format may be used, if appropriate.
- Any additional information pertinent to the evaluation of safety should also be included.

Section 12, Safety evaluation, should provide comprehensive safety information. Other sections should be concise and need not be as comprehensive as in a full report.

B. Human Pharmacokinetics, Bioavailability, and Clinical Pharmacology Studies

The ICH E3 guidance focuses on safety and efficacy trials, but notes that the basic principles and format can be applied to other kinds of trials such as clinical pharmacology trials. Additional guidance on content and format for submission of pharmacokinetics and biopharmaceutics studies is provided in the CDER document entitled *Guideline for the Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application* (February 1987). FDA

recommends that the provisions of ICH E3 and the 1987 document be applied as appropriate to clinical pharmacology and biopharmaceutics studies.

The sections included in an abbreviated clinical pharmacology and biopharmaceutics study report are the same as those described above for clinical efficacy studies. For a study with clinical pharmacology and biopharmaceutics data, the following should also be included:

- Summary tables of mean values, standard deviations or coefficients of variation, confidence intervals and observed ranges, along with sample size.

- For assay validation studies, assay performance should be summarized in enough detail for the reviewer to assess the adequacy of the assay performance including standard curve results, quality control results, specificity, accuracy, and reproducibility. There should be a reference to the full validation report for the analytical method.

- Formulation information including batch or lot numbers and qualitative and quantitative composition, and relationship to use in studies.

Published literature may be submitted in lieu of the abbreviated report. If the publication does not contain all of the items listed above, an attachment including the missing items should accompany the publication.

V. FORMAT OF A SYNOPSIS

A synopsis should contain sufficient information to allow the reviewer to assess if the results cast doubt on the safety of the product for the proposed indication. The synopsis should summarize the study including sufficient data to illustrate results. One example of the structure and content of a synopsis is described in ICH E3 (section 2). A study protocol and protocol amendments (Section 16.1.1 of ICH E3) should be provided along with the synopsis.

Generally, a complete discussion of the safety data from these studies, including all information from section 12 (Safety Evaluation) as described in ICH E3, should be included with the synopsis and/or in a separate section in the Integrated Summary of Safety. In some cases, with the agreement of the appropriate reviewing division, a complete discussion of safety may not be necessary.

Published literature may be submitted in lieu of the synopsis with supplemental safety data as appropriate. If the publication does not contain all of the information provided in a synopsis, an attachment including the missing information should accompany the publication.

VI. RECOMMENDED PROCEDURES

Applicants are encouraged to discuss with the Agency which studies should be submitted as full study reports, abbreviated reports, or synopses at the earliest possible time. Such discussions should begin during pre-IND meetings when foreign clinical trials have been completed (and the initial U.S. studies will be phase 3), and at all end-of-phase 2 and/or pre-NDA/BLA meetings for all drugs or biological products. Prior to the time of application filing, a division director may request any study to be submitted as an abbreviated or full study report if, in his/her opinion, these reports will aid in evaluating the proposed claims.

If no agreement on types of study reports to be submitted has occurred prior to filing and the Agency finds the information submitted to be insufficient on its face to evaluate safety and/or effectiveness, this inadequacy may serve as a basis to refuse to file the application [21 CFR 314.101(d)(3)]. If prefiling agreement has occurred, it is expected that Agency requests for submission of full study reports after application filing would be unusual. However, Agency staff may request additional information or data from studies submitted in an abbreviated format as questions arise during the review process.

Once the application is filed, requests for additional abbreviated reports or full study reports (other than those determined to be needed prior to filing) should be authorized by the relevant division director. Additional abbreviated study reports or full study reports should be requested within the first six months of the review cycle for standard applications and within the first three months for priority applications. Requests for additional abbreviated or full study reports made beyond these times would be extremely unusual and should be authorized by the office director. If the applicant believes that a request for additional study reports is inappropriate, the applicant should meet with the requesting official to discuss and resolve the matter. If the issues cannot be resolved at that level, an appeal may be made through the dispute resolution process.

The applicant should submit a requested abbreviated or full study report within 60 days of receiving a request (30 days for priority applications). The submitted report may be considered a major amendment for purposes of the user fee clock if submitted within 90 days prior to the user fee action date. If the requested study report is not submitted and this information is needed for the determination of safety and effectiveness of the product, this deficiency may be a basis for nonapproval of the application.

If additional guidance is needed, the applicant is directed to CDER's *Guidelines for the Format and Content of the Clinical and Statistical Section of New Drug Applications*, the ICH E3 *Structure and Content of Clinical Study Reports*, and to the appropriate review division within CDER or CBER.