Guidance for Industry

Providing Submissions in Electronic Format — Summary Level Clinical Site Data for CDER's Inspection Planning

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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

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Electronic Submissions

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Technical Specifications: The document "Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning" associated with this guidance is provided separately and will be updated periodically. To ensure that you have the most recent version, check CDER's Web page at:
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ucm332466.pdf.

Guidance for Industry[1]

Providing Submissions in Electronic Format — Summary Level Clinical Site Data for CDER's Inspection Planning

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is one in a series of guidance documents intended to assist sponsors and applicants making certain regulatory submissions to the FDA in electronic format. This guidance describes FDA's recommendation that applicants submit summary level clinical site datasets in a standardized electronic format. This guidance generally applies to submissions of summary level clinical site datasets within new drug applications (NDAs), biologics licensing applications[2] (BLAs), and NDA and BLA supplemental applications containing new clinical study reports that are submitted to CDER.

The purpose of this guidance is to assist applicants in the submission of a clinical dataset that describes and summarizes the characteristics and outcomes of clinical investigations at the level of the individual study site (summary level clinical site data). The summary level clinical site dataset is intended to facilitate use of a risk-based approach for the timely identification of clinical investigator sites for on-site inspection by CDER during the review of marketing applications. This guidance refers to a number of technical specification documents and other resources. These technical specification documents and resources are available online to make them more accessible to applicants.

FDA 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

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER)'s Office of Compliance in consultation with the Office of Biostatistics, the Office of New Drugs, the Office of Business Informatics, and the Office of Medical Policy.

[2] BLAs submitted to and reviewed by CDER as described in the *Federal Register* of June 26, 2003 (68 FR 38067), available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/UCM186799.pdf.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA is responsible for making regulatory decisions about the approval of drugs and biological products based on the Agency's review of data, including clinical safety and efficacy data, submitted in support of NDAs, BLAs, and NDA and BLA supplements.[3] Because the reliability of clinical trial data is critical to the approval decision, all CDER review disciplines share responsibility for evaluating data integrity. CDER's Office of Scientific Investigations (OSI) has specific responsibility for verifying the integrity of data submitted to CDER in support of new applications and supplements, and for determining whether clinical trials are conducted in compliance with applicable FDA regulations and statutory requirements, including those intended to ensure the rights and welfare of human research subjects.

Clinical data are a central component of most NDAs and BLAs submitted to CDER. As part of the review process, CDER may conduct on-site inspections of clinical investigators, sponsors/applicants, contract research organizations, and institutional review boards involved in clinical trials that were submitted in support of applications for product approval. During these inspections, FDA field investigators are authorized to obtain, copy, and verify records for FDA-regulated clinical trials with regard to subject case histories, and to review the storage and disposition of the investigational product under 21 CFR parts 312 and ensure that clinical data are maintained, tabulated, and submitted under the regulations provided in 21 CFR part 314.

To meet its review performance goals in accordance with CDER good review management principles and practices for products covered by the Prescription Drug User Fee Act (PDUFA), CDER must initiate inspection planning early in the application review process (during the filing determination and review planning phase).[4] CDER's inspection planning includes selection of clinical investigator sites for on-site inspections. To facilitate timely selection of inspection sites, CDER must have sufficient data from the sponsor to identify which sites will provide the necessary information for the review of the application.

As part of their NDA and BLA packages, applicants are required to submit study-specific data to FDA.[5] The submission format for these data, however, does not facilitate efficient site selection

[3] For the purposes of this guidance, all references to drugs include both human drugs and therapeutic biological products regulated by CDER.

[4] See the FDA guidance for review staff and industry on *Good Review Management Principles and Practices for PDUFA Products*. Agency guidance on electronic submissions will be updated regularly to reflect the evolving nature of the technology and the experience of those using this technology. To ensure that you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[5] See 21 CFR 314.50(d)(5) (clinical data) and 314.50(f) (case report forms and tabulations).

because these data are submitted as subject level data.[6] CDER has determined that to plan efficiently for clinical site inspections and to meet the PDUFA goal dates for marketing applications, CDER prefers to receive summary level clinical site data.

In an effort to provide a more timely approach to site selection, CDER recently initiated a pilot program evaluating a risk-based model for selecting clinical investigator sites for inspection. The model is based on an array of risk parameters across clinical investigator sites associated with marketing applications. The model uses a structured dataset — a summary level clinical site dataset — that describes and summarizes the characteristics and outcomes of clinical investigations at the level of the individual study site. Initial experience with the pilot program suggested that a risk-based model using a structured dataset may facilitate more efficient site selection. CDER anticipates that site inspections will be conducted earlier in the review cycle using this site selection model. The use of this model will be advantageous because it facilitates good review management practices as described in the *CDER 21st Century Review Process Desk Reference Guide*.[7] We also expect that this risk-based model will provide applicants with an opportunity to address regulatory issues identified during these inspections earlier in the review process.

To enable CDER to implement a risk-based approach to inspections, to plan inspections efficiently and effectively, and to meet PDUFA goal dates, the Center recommends that applicants submit summary level clinical site data, as described further below.

III. DESCRIPTION OF SUMMARY LEVEL CLINICAL SITE DATASET

A summary level clinical site dataset contains data from all relevant studies used to support evaluation of the application, including studies that support various treatment indications. The summary level clinical site dataset is intended to (1) characterize individual clinical investigator sites, (2) describe aspects of the studies with which those clinical investigator sites are associated, and (3) present the characteristics and outcomes of the study at the site level. The summary level clinical site dataset provides critical information in a usable format to assist in site selection.

The data requested in the electronic summary level clinical site dataset comprise data elements collected under regulations in part 312 (specifically in § 312.62(b) (Case histories) and § 312.64 (Investigator Reports)) and maintained, tabulated, and submitted under regulations in part 314

[6] For a description of the submission format that sponsors generally use, see the International Conference on Harmonisation (ICH) guidance for industry *E3 Structure and Content of Clinical Study Report*. The ICH *E3 Structure and Content of Clinical Study Report* provides recommendations on the general content and structure of a core clinical study report, but may be adapted by sponsors to meet the requirements of individual regulatory authorities or to better display or communicate study information.

[7] See the *CDER 21st Century Review Process Desk Reference Guide*, available at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

(specifically in § 314.50(d)(5) (Clinical data section) and § 314.50(f) (Case report forms and tabulations)) or in part 601 (specifically in § 601.2 (Applications for Biologic Licenses; procedures for filing)). To ensure the submission of complete information organized in a format that facilitates site selection, CDER recommends that applicants use the structured approach described in this guidance, and the associated technical specifications in the document "Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning," when submitting a summary level clinical site dataset.[8]

A single summary level clinical site dataset should contain data from all major (e.g., pivotal) studies used to support safety and efficacy in the application, including studies with different treatment indications. For each major study used to support safety and efficacy, data should be submitted by clinical site and treatment arm for the intent-to-treat (ITT) population. For clinical investigator sites involved in multiple studies in support of an application, applicants should provide the data independently for each study within the dataset. When in doubt about what constitutes a "major" study, applicants should consult the relevant review division.

IV. WHEN TO SUBMIT A SUMMARY LEVEL CLINICAL SITE DATASET

CDER recommends that applicants submit a summary level clinical site dataset with all NDAs, BLAs, or supplements that contain clinical data, preferably with the NDA/BLA submission.[9] Alternatively, a summary level clinical site dataset can be provided for a pre-NDA or pre-BLA meeting. This dataset should include data for each major (e.g., pivotal) clinical study submitted to support safety and efficacy. Summary level site data are not requested for biopharmaceutic, clinical pharmacology, or animal studies. Reviewers in the OSI are available to assist applicants with questions about submitting these summary level clinical data.

[8] Several final and draft guidances for industry are available that discuss issues common to various types of electronic regulatory submissions, such as acceptable file formats, media, and submission procedures, and offer recommendations for file formats, fonts, and electronic transmission of files. See, e.g., FDA's guidance for industry *Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at section III.E.4 (Module 5 Clinical Study Reports Folder; Datasets). See also "Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning" for details on providing datasets and related files (e.g., data definition files, program files), available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf. In an application submitted as an electronic common technical document (eCTD), the summary level clinical site dataset would be placed in Module 5. See the ICH guidances for industry *M4E: The CTD — Efficacy* and *M2 eCTD: Electronic Common Technical Document Specification*. The eCTD specifications are available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

[9] In the event that a new clinical dataset is submitted in the review cycle, this information should also be included as part of the summary level clinical site dataset.

A. Pre-NDA or Pre-BLA Meeting

Before submitting applications, many sponsors request a pre-NDA or pre-BLA meeting with FDA. The presubmission meeting generally occurs when all studies designed to support the proposed indications have been completed. During this meeting, sponsors should consider discussing with FDA their intention to submit summary level clinical site datasets in the format described in this guidance. When submission of the NDA or BLA will occur shortly after the pre-NDA or pre-BLA meeting and the final site level data are available, sponsors should consider providing the summary level clinical site dataset before submitting the NDA or BLA.

B. With the Application or Supplement

Applicants that did not participate in a pre-NDA/BLA meeting, or did not submit the summary level clinical site dataset in advance of their NDA/BLA submission, should submit the summary level clinical site dataset with the application or supplement.

V. CREATING AND SUBMITTING THE DATA FILE

The summary level clinical site dataset should be submitted in the format described in the document "Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning." This technical specifications document is provided separately and will be updated periodically. To ensure that you have the most recent version, check CDER's Web page at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf.

A summary level clinical site dataset submitted with an application in the eCTD format should be included in Module 5 – Clinical Study Reports. The technical specifications document also describes the variables for the clinical site dataset and includes a sample data submission.

Applicants are encouraged to discuss with CDER the submission of datasets that might have missing variables.

A. Data Elements for the Data File

The data elements currently accepted by CDER for electronic submission of the summary level clinical site dataset are presented in "Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning."[10]

B. Electronic Transport Format

[10] See the Study Data Specifications that provide general recommendations for submission of datasets in electronic format (http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf).

The summary level clinical site data should be submitted in the transport file format identified in "Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning."

C. Submitting the Summary Level Clinical Site Dataset

The summary level clinical site data file can be submitted electronically through the FDA Electronic Submission Gateway (ESG) or using appropriate physical media. For information on submitting the dataset, see the "Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning." See also Specification for Transmitting Electronic Submissions using eCTD Specifications (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163567.pdf).