Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions

Guidance for Industry

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 associated with this guidance are provided as a separate document and are updated periodically:

- ***Bioresearch Monitoring Technical Conformance Guide***

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Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions Guidance for Industry[1]

I. INTRODUCTION

This guidance finalizes the draft guidance of the same title dated February 2018.[2] This guidance describes the electronic submission of certain data and information in standardized formats and applies to electronic submissions of data and information from all major (i.e., pivotal) studies[3] used to support safety and efficacy claims in new drug applications (NDAs), biologics license applications (BLAs)[4] regulated by the Center for Drug Evaluation and Research (CDER), and supplements containing new clinical study reports. It also applies when these data and information are submitted in certain investigational new drug applications[5] (INDs) in advance of a planned NDA, BLA, or supplement submission.

CDER uses the data and information described in this guidance to plan bioresearch monitoring (BIMO) inspections[6] to facilitate the timely identification of sites for inspection and to ensure that field investigators from the Food and Drug Administration's (FDA or Agency) Office of Inspections and Investigations (OII) (formerly Office of Regulatory Affairs), which is the office responsible for the conduct of the inspections, have the information needed to conduct the

[1] This guidance has been prepared by the Office of Compliance in the Center for Drug Evaluation and Research in consultation with the Office of Translational Sciences, the Office of Biostatistics, the Office of New Drugs, and the Office of Business Informatics at the Food and Drug Administration.

[2] See 83 FR 7043 (Feb 16, 2018). The draft guidance superseded the previously issued draft guidance for industry *Providing Submissions in Electronic Format — Summary Level Clinical Site Data for CDER's Inspection Planning* (December 2012).

[3] For questions regarding whether a study is considered major (i.e., pivotal), applicants should consult the relevant review division.

[4] This guidance applies only to BLAs regulated by the Center for Drug Evaluation and Research. See "Drug and Biological Product Consolidation" in the *Federal Register* of June 26, 2003 (68 FR 38067), available at https://www.federalregister.gov/documents/2003/06/26/03-16242/drug-and-biological-product-consolidation.

[5] See the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (September 2024) (eCTD Guidance). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] See section 704(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 374(a)) and 21 CFR 312.58 (sponsors and contract research organizations), 312.68 (clinical investigators), 312.120(a)(ii), and 314.106(b) (foreign studies not conducted under an IND).

inspections.[7] Twenty-four months after the issuance of this guidance, the data in NDAs and BLAs described in this guidance must be submitted electronically in the format specified in this guidance.[8]

In section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), Congress granted explicit authorization to FDA to specify, in guidance, the electronic format for submissions under section 505(b), (i), or (j) of the FD&C Act (21 U.S.C. 355(b), (i), or (j)) and submissions under section 351(a) or (k) of the Public Health Service Act (42 U.S.C. 262(a) or (k)). Accordingly, to the extent that this document provides such requirements, as indicated by the use of the words *must* or *required*, this document is not subject to the usual restrictions in FDA's good guidance practice (GGP) regulations, such as the requirement that guidances not establish legally enforceable responsibilities. See 21 CFR 10.115(d).

To comply with GGP regulations and make sure that regulated entities and the public understand that guidance documents are nonbinding, FDA guidances ordinarily contain standard language explaining that guidance documents should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. FDA is not including this standard language in this guidance document because it is not an accurate description of this guidance. Insofar as this guidance specifies the format for electronic submissions pursuant to section 745A(a) of the FD&C Act, it will have binding effect.

II. BACKGROUND

A. Electronic Submissions to FDA Under Section 745A(a) of the FD&C Act

The guidance for industry *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* (December 2014) (745A(a) Implementation Guidance) sets forth general information on how FDA interprets and intends to implement the electronic submission requirements of section 745A(a) of the FD&C Act. The 745A(a) Implementation Guidance states that it is not feasible to describe and implement the electronic format(s) that would apply to all the submissions covered by section 745A(a) in one guidance document. Instead, FDA will periodically issue guidances specifying the electronic format for certain types of submissions. The guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (September 2024) (eCTD

[7] For questions regarding information to submit for a clinical investigator site in a decentralized clinical trial (also referred to as *clinical site* in this guidance), applicants should consult the relevant review division.

[8] See section 745A(a) of the FD&C Act (21 U.S.C. 379k–1(a)) and the guidance for industry *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* (December 2014).

Guidance) specifies the general format for certain types of electronic submissions using the electronic common technical document (eCTD), including the specifications for Module 5.[9]

In addition to the more general information and implementation timelines found in those guidances, this guidance provides information regarding the format to be used for electronic submission of NDA and BLA content for the planning and conduct of CDER BIMO inspections, using eCTD.

B. NDA and BLA Content for BIMO

FDA is responsible for making regulatory decisions about the approval of marketing applications and supplements for drugs and biological products, based, among other things, on the Agency's review of data, including clinical safety and efficacy data, submitted in support of NDAs, BLAs, and NDA and BLA supplements.[10] Section 314.50 (21 CFR 314.50) describes the general content and format of NDAs and supplements, and includes the following requirements:

> An NDA for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling, including, if applicable, any Medication Guide required under part 208 of this chapter. Other NDAs will generally contain only some of those items, and information will be limited to that needed to support the particular submission. These include an NDA of the type described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, an amendment, and a supplement. The NDA is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source.[11]

Section 314.50(d) describes the technical sections of an application and requires that each technical section "contain data and information in sufficient detail to permit the [A]gency to make a knowledgeable judgment about whether to approve the NDA or whether grounds exist under section 505(d) of the Federal Food, Drug, and Cosmetic Act to refuse to approve the NDA." Requirements for the clinical data technical section of the application are described in § 314.50(d)(5), including the following sections of particular pertinence to this guidance:

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[9] The current version of the associated technical specification entitled *The eCTD Backbone Files Specification for Module 1* provides additional information. See FDA's eCTD web page at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

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

[11] Similarly, § 601.2(a) (21 CFR 601.2(a)) describes the general content and format of BLAs and supplements. ("To obtain a biologics license under section 351 of the Public Health Service Act for any biological product, the manufacturer shall submit an application to the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research . . . on forms prescribed for such purposes, and shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency" (§ 601.2(a)).

- Requirements for inclusion of a description of, and certain other information regarding, each controlled (see § 314.50(d)(5)(ii)) and uncontrolled clinical study (see § 314.50(d)(5)(iii)). Section 314.50(d)(5)(ii) further specifies that the clinical data section of the application "includ[es] the protocol and a description of the statistical analyses used to evaluate the study."

- Requirement for:

  > [a] description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the NDA, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.[12]

- Requirement that:

  > [i]f a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement [be included] containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer — in lieu of a listing of the specific obligations transferred — may be submitted.[13]

In addition, § 314.50(f) describes requirements for submission of case report forms and tabulations. Case report forms and tabulations, as discussed in § 314.50(f), include study data tabulations, statistical analysis datasets, data listings, and subject profiles. Specifically, as pertinent to this guidance:

- Section 314.50(f)(1) states that:

  > [t]he NDA is required to contain tabulations of the data from each adequate and well-controlled study under § 314.126 (Phase 2 and Phase 3 studies as described in §§ 312.21 (b) and (c) of this chapter), tabulations of the data from the earliest clinical pharmacology studies (Phase 1 studies as described in § 312.21(a) of this chapter), and tabulations of the safety data from other clinical studies. Routine submission of other patient data from uncontrolled studies is not required. The tabulations are required to include the data on each patient in each study, except that the applicant may delete those tabulations which the [A]gency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness.

- Section 314.50(f)(3) states that "[t]he applicant must submit to FDA additional case report forms and tabulations needed to conduct a proper review of the NDA, as requested by the director of the FDA division responsible for reviewing the NDA."

[12] Section 314.50(d)(5)(iv).

[13] Section 314.50(d)(5)(x).

Because the reliability of clinical study data is critical to the approval decision, all CDER review disciplines share responsibility for evaluating data integrity. CDER's Office of Scientific Investigations (OSI), in the Office of Compliance, has specific responsibility for verifying the integrity of data submitted to CDER in support of original applications and supplements containing new clinical study reports, and for determining whether clinical studies 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 request OII investigators conduct on-site inspections of clinical investigators, sponsors/applicants, contract research organizations, and institutional review boards involved in clinical studies that were submitted in support of applications for drug approval.[14] During these inspections, OII investigators may obtain, copy, and verify records for FDA-regulated clinical trials with regard to, among other things (1) subject case histories; (2) storage and disposition of the investigational drug under 21 CFR part 312; and (3) clinical data to ensure they are maintained, tabulated, and submitted in compliance with the regulations in parts 312 and 314 (21 CFR parts 312 and 314).[15]

To meet its review performance goals in accordance with CDER good review management principles and practices for drugs covered by the Prescription Drug User Fee Act (PDUFA), CDER generally initiates inspection planning early in the application review process (i.e., during the filing determination and review planning phase).[16] CDER's inspection planning includes (1) the selection of clinical investigator sites and other regulated entities for on-site inspections and (2) the preparation of assignment memos and background packages that are provided to OII investigators who perform FDA's BIMO inspections. The following data from NDAs, BLAs, and supplements containing new clinical study reports are used to facilitate the timely planning and conduct of inspections:

- Identification of all entities that sponsors have contracted to conduct clinical study-related activities, regardless of whether sponsors have transferred regulatory obligations for the conduct of those activities

- Locations of clinical study-related documentation (applicant/sponsor/contract research organization records)

- Locations of clinical investigator sites

[14] See section 704(a) of the FD&C Act and 21 CFR 56.115, 312.52(b), 312.58, 312.68, 312.120(a)(1)(ii), and 314.106(b).

[15] See 21 CFR 312.57, 312.58(a), 312.62, and 314.50.

[16] See the guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products* (April 2005).

- Case report tabulations of data for each subject in each study that are needed to conduct a proper review of the application

In addition, in an effort to provide a more timely approach to site selection, CDER has developed a risk-based model to select clinical investigator sites for inspection. The model uses an array of risk parameters across clinical investigator sites associated with marketing applications. To facilitate site selection, the model uses a summary-level clinical site dataset that describes and summarizes the characteristics and outcomes of clinical investigations, both at the study level and at the level of the individual study site. CDER anticipates that the risk-based model will provide for earlier identification of clinical investigator sites for inspection and, therefore, that these inspections will be conducted earlier in the review cycle. Using the risk-based site selection model is advantageous because it facilitates good review management practices, as described in the *CDER 21st Century Review Process Desk Reference Guide*.[17] The completion of inspections earlier in the review cycle also provides applicants the opportunity to address significant inspection observations earlier in the process.

Study-specific data (both clinical study-level information and clinical site data)[18] submitted to FDA as part of NDAs, BLAs, and supplements containing new clinical study reports are described below in section III. The required electronic format for these submissions is described below in section IV, and in the accompanying technical specifications document *Bioresearch Monitoring Technical Conformance Guide*. This technical specifications document is provided separately and will be updated periodically.[19]

III. DESCRIPTION OF CLINICAL STUDY-LEVEL INFORMATION, SUBJECT-LEVEL DATA LINE LISTINGS BY CLINICAL SITE, AND SUMMARY-LEVEL CLINICAL SITE DATASET

Reviewers from OSI, the Office of New Drugs (OND), and the Office of Biostatistics rely on timely access to accurate data in NDA and BLA submissions to issue inspection assignments as early in the review process as possible. This is important to ensure that inspection results are available:

(1) To inform OSI's assessment of data integrity and human subject protection
(2) To make recommendations to OND regarding data reliability
(3) To permit time for the applicant to address any significant inspection findings

In the past, applicants have frequently provided this information in variable data formats that are not conducive to timely inspection planning or conduct of inspections. Therefore, a consistent

[17] See the *CDER 21st Century Review Process Desk Reference Guide*, available at https://www.fda.gov/media/78941/download.

[18] See, for example, § 314.50(d)(5) (clinical data) and § 314.50(f) (case report forms and tabulations).

[19] See the technical specifications document *Bioresearch Monitoring Technical Conformance Guide.* For the most recent version, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

process for submitting data and information used for routine BIMO inspections is critical to meet the PDUFA timeline goals. To accelerate the process of inspection planning, including the identification of inspection sites, FDA relies on the items described below in NDAs, BLAs, and NDA and BLA supplements containing major (i.e., pivotal) study reports used to support safety and efficacy claims.

Additional specifications, recommendations, and general considerations for the electronic format of the submission of the items described in sections III.A, III.B, and III.C of this guidance are provided in the technical specifications document *Bioresearch Monitoring Technical Conformance Guide*.[20]

A. Clinical Study-Level Information

The items described in this section are used to facilitate inspection planning, including site selection, and the conduct of inspections.

1. A Comprehensive and Readily Located Table Listing All Clinical Sites That Participated in Clinical Studies

Information concerning clinical sites that consent, screen, and enroll trial subjects in clinical studies is relied on to inform the selection of sites for inspection. Accurate contact information is also important because it enables OII to contact clinical investigators to schedule inspections and to ensure that inspections are directed to occur at the correct location (i.e., where records are available for review).

For each study, the applicant should generate a table that includes the name of the clinical investigator at each site, the site identification number, the site address (street address, city, state, and country), and contact information for the site (phone number, fax number (when available), and email address (when available)).

2. A Table Listing All Entities to Which the Sponsor Has Contracted Clinical Study-Related Activities[21]

Information concerning clinical study-related activities for major (i.e., pivotal) studies that have been contracted to other entities is also relied on to inform the selection of sites for inspection, and includes a description of the following:

- All entities the sponsor(s) of these studies contracted to conduct study-related activities
- For each entity, the study-related activities that were contracted, including whether the sponsor transferred responsibility for the regulatory obligations applicable to those activities

[20] See footnote 19.

[21] See 21 CFR 312.23(a)(1)(viii), 312.52, and 314.50(d)(5)(x).

For example, the sponsor may transfer responsibilities in a clinical study for study-related activities including, but not limited to, clinical site monitoring, randomization, and drug distribution.

3. Protocol, Protocol Amendments, and Annotated Case Report Form(s)

The protocol, protocol amendments, and copy of the associated annotated case report form(s) for major (i.e., pivotal) studies used to support safety and efficacy in the application are relied on for the conduct of inspections.[22]

B. Subject-Level Data Line Listings by Clinical Site

To verify key study data during inspections, subject-level data line listings by clinical site are provided to OII investigators. By-site listings for major (i.e., pivotal) studies, including studies with different treatment indications, include listings for each clinical site that consented subjects and contain primary data points in addition to derived data. For example, for a pain trial in which subjects recorded pain scores in a diary, the actual diary scores (i.e., the raw data) are primary data points that were used to calculate the derived primary endpoint and any other derived protocol elements (e.g., an eligibility criterion).

C. Summary-Level Clinical Site Dataset

The summary-level clinical site dataset, named *clinsite*, contains data from major (i.e., pivotal) studies used to support safety and efficacy claims and is intended:

(1) To characterize individual clinical investigator sites
(2) To describe aspects of the studies associated with those clinical investigator sites
(3) To present the characteristics and outcomes of the study at the site level

The summary-level clinical site dataset, submitted in the exchange format described in the *FDA Data Standards Catalog* for clinical study datasets, provides critical information to assist with site selection.[23, 24]

The data in the summary-level clinical site dataset comprise data elements collected under the regulations in part 312 (specifically in 21 CFR 312.62(b), case histories, and 21 CFR 312.64, investigator reports) and maintained, tabulated, and submitted under the regulations in part 314 (specifically in § 314.50(d)(5), clinical data section, and § 314.50(f), case report forms and tabulations) or in 21 CFR part 601 (specifically in §§ 601.2 and 601.14(a), applications for biologics licenses; procedures for filing).

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[22] See § 314.50(d).

[23] For required data formats, see the *FDA Data Standards Catalog*, available at https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm.

[24] For additional information on data formats, see the guidance for industry *Providing Regulatory Submissions in Electronic Format — Standardized Study Data* (June 2021).

A single summary-level clinical site dataset contains data from all major (i.e., pivotal) studies used to support safety and efficacy in the application, including studies with different treatment indications. The dataset includes data independently for each study when clinical investigator sites are involved in multiple studies in support of an application. Summary-level site data are not requested for biopharmaceutical, clinical pharmacology, or animal studies.

IV. SUBMITTING CLINICAL STUDY-LEVEL INFORMATION, SUBJECT-LEVEL DATA LINE LISTINGS BY CLINICAL SITE, AND SUMMARY-LEVEL CLINICAL SITE DATASET

The clinical study-level information, subject-level data line listings by clinical site, and summary-level clinical site dataset files submitted with NDAs, BLAs, and NDA and BLA supplements containing new clinical study reports must be submitted electronically by using the FDA Electronic Submissions Gateway or by using appropriate physical media.[25]

Clinical study-level information, subject-level data line listings by clinical site, and the summary-level clinical site dataset submitted with an application, in eCTD format, are placed in CTD Module 5 (M5) — Clinical Study Reports. More information on submitting these data elements is provided in the technical specifications document *Bioresearch Monitoring Technical Conformance Guide*.[26]

[25] See the eCTD Guidance. See also the technical specifications document *Transmitting Electronic Submissions Using eCTD Specifications,* available at https://www.fda.gov/media/76812/download.

[26] See footnote 19.