Standardized Format for Electronic Submission for Marketing Applications Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for Center for Biologics Evaluation and Research Submissions

Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

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

For the most current version of this document, refer to the web page at:
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioresearch-monitoring-technical-conformance-guide

Contains Nonbinding Recommendations

Draft – Not for Implementation

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Standardized Format for Electronic Submission for Marketing Applications Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for Center of Biologics Evaluation and Research Submissions

Draft Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This draft guidance applies to electronic submissions of data and information from the major (i.e., pivotal) studies[2] used to support safety and efficacy claims in biologics license applications (BLAs) and new drug applications (NDAs) regulated by the Center for Biologics Evaluation and Research (CBER), as well as supplemental applications containing new clinical study reports. It also applies when these data and information are submitted in certain investigational new drug applications (INDs)[3] in advance of a planned BLA, NDA, or supplemental submission. This draft guidance, when finalized, will contain the same data and information requirements described in the Center for Drug Evaluation and Research (CDER) draft *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions Guidance for Industry*, when finalized.[4]

CBER uses the data and information described in this guidance to plan bioresearch monitoring (BIMO) inspections,[5]including to facilitate the timely identification of sites for inspection and to ensure that field investigators from the Food & Drug Administration's (FDA or Agency) Office of Regulatory Affairs (ORA), which is the office responsible for the conduct of the inspections,

[1] This guidance has been prepared by the Office of Compliance and Biologics Quality in the Center for Biologics Evaluation and Research.

[2] For questions regarding whether a study is considered major, applicants should consult the relevant review division.

[3] See FDA guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*

[4] This draft guidance was published in February 2018.

[5] 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).

have the information needed to conduct the inspections. Twenty-four months after this draft guidance has been finalized, the data in BLAs and NDAs, and supplemental applications described in this guidance must be submitted electronically in the format specified in this guidance.[6]

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 (PHS 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 Federal Food, Drug, and Cosmetic Act

The 745A(a) Implementation Guidance[7] 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 FDA guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (eCTD Guidance) specifies the general

[6] See section 745A(a) of the FD&C Act and FDA guidance for industry *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* (745A(a) Implementation Guidance).

[7] See the FDA guidance for industry *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act*, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-submissions-under-section-745aa-federal-food-drug.

format for certain types of electronic submissions using the Electronic Common Technical Document (eCTD), including the specifications for Module 5.[8]

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

B. BLA and NDA Content for BIMO

FDA is responsible for making regulatory decisions about the approval of marketing applications and supplements for biological and drug products, based, among other things, on the Agency's review of data, including clinical safety and efficacy data, submitted in support of BLAs, NDAs and BLA and NDA supplements. Section 601.2 (21 CFR 601.2(a)) describes the general content and format of BLAs and supplements, and includes the following requirements:

> 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 (see mailing addresses in § 600.2(a) or (b) of this chapter), 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.

Section 314.50 (21 CFR 314.50) describes the general content and format of NDAs and supplements, and includes the following requirements:

> An application 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 applications will generally contain only some of those items, and information will be limited to that needed to support the particular submission. These include an application of the type described in section 505(b)(2) of the [FD&C Act], an amendment, and a supplement. The application 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 application that is received or otherwise obtained by the applicant from any source.

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

Section 314.50(d) describes the technical sections of an NDA 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 application or whether grounds exist under section 505(d) of the [FD&C Act] to refuse to approve the application." 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:

1. Requirements for inclusion of a description of, and certain other information regarding, each controlled (§ 314.50(d)(5)(ii)) and uncontrolled clinical study (§ 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."

2. 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 application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers [see § 314.50(d)(5)(iv)].

3. Requirement for:

   [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 [see § 314.50(d)(5)(x)].

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 patient profiles.[9] Specifically, as pertinent to this guidance:

[9] See "Study Data Technical Conformance Guide" at https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm#guides

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

   [t]he application 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.

2. 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 application, as requested by the director of the FDA division responsible for reviewing the application."

Because the reliability of clinical trial data is critical to the approval decision, all CBER review disciplines share responsibility for evaluating data integrity. CBER's Bioresearch Monitoring Branch (BMB) of the Division of Inspection and Surveillance (DIS), in the Office of Compliance and Biologics Quality (OCBQ), has specific responsibility for verifying the integrity of data submitted to CBER in support of 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 BLAs and NDAs submitted to CBER. As part of the review process, CBER may request ORA investigators 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.[10] During these inspections, ORA 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 product 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) and 21 CFR 601.2.[11]

To meet its review performance goals in accordance with CBER good review management principles and practices for products covered by the Prescription Drug User Fee Act (PDUFA), CBER generally initiates inspection planning early in the application

[10] 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).
[11] See §§ 312.57, 312.58(a), 312.62, and 314.50.

review process (i.e., during the filing determination and review planning phase).[12] CBER'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 ORA investigators that perform FDA's BIMO inspections. The following data from BLAs, NDAs and supplements are used to facilitate the timely planning and conduct of inspections:

1. Identification of all entities to which sponsors have transferred regulatory obligations for clinical trial-related activities.

2. Locations of clinical study-related documentation (Applicant/Sponsor/Contract Research Organization records).

3. Locations of clinical investigator sites.

4. Case report tabulations of data for each patient 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, CBER plans to use 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, at the study level, individual study site level, and at the level of the individual study subject. CBER 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. 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)[13] submitted to FDA as part of BLA and NDA packages are described below in section III. The required electronic format for these submissions is described in section IV, below, and the accompanying Bioresearch Monitoring Technical Conformance Guide[14].

[12] See the FDA guidance for review staff and industry *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.
[13] See, e.g., § 314.50(d)(5) (clinical data) and § 314.50(f) (case report forms and tabulations).
[14] The current version of the Bioresearch Monitoring Technical Conformance Guide is available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioresearch-monitoring-technical-conformance-guide

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

Reviewers from BMB, the Office of Vaccines Research and Review, Office of Therapeutic Products, Office of Blood and Research Review, and the Office of Biostatistics and Pharmacovigilance rely on timely access to accurate data in BLA and NDA 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 BMB's assessment of data integrity and human subject protection;
(2) To make recommendations regarding data reliability; and
(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. A consistent process for submitting data and information used for routine BIMO inspection planning is therefore critical to meet the PDUFA timeline goals. To accelerate the process of inspection planning, including the identification of inspection sites, FDA relies on the following items in BLAs, NDAs, and BLA and NDA supplemental applications containing major study report[s] and dataset[s] used to support safety and efficacy claims in the application.

Specifications 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 Bioresearch Monitoring Technical Conformance Guide. This technical specification document is provided separately and will be updated periodically.

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 participated in clinical studies is relied on to inform the selection of sites for inspection. Accurate contact information is also important because it enables ORA 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 e-mail address (when available)).

2. *A Table Listing All Entities to Whom the Sponsor Has Transferred or Contracted Clinical Study-Related Activities*[15]

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

- All entities to which the sponsor(s) of these studies transferred responsibility under contract for any or all of their regulatory responsibilities.

- The study functions that were contracted without a transfer of regulatory obligations.

For example, contracted responsibilities in a clinical trial may include, but are 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 Study Data Tabulation Model (SDTM) annotated case report form(s) for major studies used to support safety and efficacy in the application are relied on for the conduct of inspections.[16]

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 ORA investigators. By-site listings for major 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," for data submission and tracking purposes, contains data from major (i.e., pivotal) studies used to support safety and efficacy claims in an application and is intended:

[15] See §312.23(a)(1)(viii), §312.52, and §314.50(d)(5)(x).
[16] See § 314.50(d).

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

The summary-level clinical site dataset, submitted in the format described in the FDA Data Standards Catalog, provides critical information to assist with site selection.[17]

The data in the summary-level clinical site dataset comprise data elements collected under the regulations in part 312 (specifically in § 312.62(b), case histories, and § 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; regulatory submissions in electronic format).

A single summary-level clinical site dataset contains data from all major 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 supplemental applications must be submitted electronically by using the FDA Electronic Submission Gateway (ESG) or by using appropriate physical media.[18]

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. This technical specifications document is provided separately and will be updated periodically.

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

[18] See the FDA guidance for industry *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. See also the technical specifications document *Transmitting Electronic Submissions Using eCTD Specifications,* available at https://www.fda.gov/media/76812/download.