Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Ebla Ali Ibrahim, 301-796-3691, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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

July 2019
Electronic Submissions
Revision 7

Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

Guidance for Industry

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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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RELATED DOCUMENTS

Technical specifications associated with this guidance are provided as separate documents and are updated periodically. Documents cited within this guidance are provided at the end of this document.

For a complete listing of all documents and supportive files needed to submit electronically, refer to the eCTD web page at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

REVISION HISTORY

DATE	SUMMARY OF REVISIONS
April 2017	**Update to Guidance** Section I. Introduction • Added paragraph describing rationale for changing timetable for required master file submissions in eCTD from 24 months to 36 months Section III.B. Timetable for Implementation of Electronic Submission Requirements • Updated section to reflect that the requirement for master files to be filed electronically takes effect 36 months after May 5, 2015 • Updated example of timetable to reflect actual timetable for the implementation of the electronic submissions requirement
April 2018	**Update to Guidance** Section I. Introduction • Added paragraph describing rationale for extending timetable for Type III drug master file submissions in eCTD for an additional 12 months Section III.A. Types of Submissions That Must Adhere to the Electronic Submission Requirement Described in This Guidance • Revised paragraph to reflect change in nomenclature of "biologic product files (BPFs)" to "other master files relevant to a biological product" Section III.B. Timetable for Implementation of Electronic Submission Requirements • Updated section to reflect that the requirement for Type III drug master files to be filed electronically takes place 48 months after May 5, 2015 • Updated example of timetable to reflect actual timetable for the implementation of the electronic submissions requirement

January 2019	Section I. Introduction • Added paragraph describing rationale for extending timetable for Type III drug master file submissions in eCTD for an additional 12 months Section III.B. Timetable for Implementation of Electronic Submission Requirements • Updated section to reflect that the requirement for Type III drug master files to be filed electronically takes place 60 months after May 5, 2015 • Updated example of timetable to reflect actual timetable for the implementation of the electronic submissions requirement
July 2019	**Update to Guidance** Section I. Introduction • Added paragraph describing the addition of exemptions and waivers from complying with eCTD requirements Section III.C. Types of Submissions That Are Exempted From the eCTD Requirement Described in This Guidance • Updated section to include exemption for Type III drug master files Section III.D. Types of Submissions That May Qualify for a Long-Term Waiver From the eCTD Requirement Described in This Guidance • Added section to include waiver criteria for certain PET drug INDs, NDAs, ANDAs, and BLAs, and waiver criteria for certain Type II DMFs Section III.E. Types of Submissions That May Qualify for a Short-Term Waiver From the eCTD Requirement Described in This Guidance • Added section to include the criteria to qualify for a waiver and the instructions on how to submit a request for a short-term waiver

TABLE OF CONTENTS

Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product[1] Applications and Related Submissions Using the eCTD Specifications

Guidance for Industry[2]

I. INTRODUCTION

Under section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), at least 24 months after the issuance of a final guidance document in which the Food and Drug Administration (FDA or Agency) has specified the electronic format for submitting submission types to the Agency, such content must be submitted electronically and in the format specified by FDA.[3,4,] This guidance describes how sponsors and applicants must organize the content that they submit to the Agency electronically for all submission types under section 745A(a) of the FD&C Act. This guidance also references several technical specification documents[5] and the Electronic Common Technical Document Conformance (eCTD) Guide, which provide additional details regarding the organization of content for electronic submissions.[6]

[1] The term *human pharmaceutical product*, as used in this guidance, includes any product intended for human use that meets the definition of drug and does not also meet the definition of *device* under the Federal Food, Drug, and Cosmetic Act (FD&C Act), including both drugs approved under the FD&C Act and biological products approved under the Public Health Service Act (PHS Act). Similarly, for the purposes of this document, unless otherwise specified, the term drug refers to human prescription drugs, including those that are licensed as biological products (biologics).

[2] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

[3] See 21 USC 379k–1

[4] For additional information on how FDA interprets and intends to implement the electronic submission requirements of section 745A(a) of the FD&C Act, please see 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). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[5] For instance, to reflect the evolving nature of the technology and the experience of those using this technology, the electronic common technical document (eCTD) technical specifications are being provided as separate documents in connection with this guidance. These associated specifications will be updated periodically. For the most recent versions of related technical specifications (CDER and CBER), check the eCTD web page at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

[6] For the most recent version of the eCTD Technical Conformance Guide, check the eCTD Resources web page at https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm535180.htm.

This guidance implements the electronic submission requirements of section 745A(a) of the FD&C Act for the electronic format of the content submitted in new drug applications (NDAs), abbreviated new drug applications (ANDAs), certain biologics license applications (BLAs), and certain investigational new drug applications (INDs) to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). See section III.A of this document for more information regarding required submission types. Submissions that are not submitted electronically and electronic submissions that are not in a format that FDA can process, review, and archive will not be filed or received unless they have an exemption or waiver from the electronic submission requirements.

The revision of this guidance that posted on May 5, 2015, provided a timetable of 24 months after issuance of the final guidance for the initial implementation of the electronic submission requirement for NDAs, ANDAs, BLAs, and master files (May 5, 2017) and 36 months for commercial INDs (May 5, 2018). The timetable indicated that NDAs, BLAs, ANDAs, and master files were to be submitted electronically in eCTD format starting on May 5, 2017 (May 5, 2018, for commercial INDs). Subsequently, in response to industry comments and internal review, FDA extended the implementation date for drug master files (DMFs) to 36 months (to May 5, 2018) (Revision 4) and the implementation date for Type III DMFs to 48 months (May 5, 2019) (Revision 5). Since publication of Revision 5, FDA determined that many of the concerns outlined above remain. Therefore, the Agency issued a revision to this guidance to further extend the implementation date for Type III DMFs until May 5, 2020 (Revision 6).

This revision to the guidance (Revision 7) modifies previous versions by including exemptions for Type III DMFs (see section III.C). In addition, this guidance has been updated to include the criteria identifying those types of submissions that may qualify for a long-term waiver (see section III.D) or a short-term waiver (see section III.E) from the eCTD submission requirement and instructions on how to submit a waiver request.

II. BACKGROUND

In section 745A(a) of the FD&C Act, Congress granted explicit authorization to FDA to implement the statutory electronic submission requirements in guidance and required that FDA "shall" issue such guidance. Accordingly, as indicated by 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); see also 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) (the 745A(a) Implementation Guidance)).

To comply with the 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 because it is not an accurate description of all the effects of this

guidance. Insofar as this document specifies the format for electronic submissions or provides "criteria for waivers of and exemptions" from the requirements of section 745A(a) of the FD&C Act, it will have binding effect.

III. REQUIREMENT TO SUBMIT ELECTRONICALLY UNDER THIS GUIDANCE

As of May 5, 2017, sponsors and applicants must submit the content for which an electronic format for submission is specified in this guidance in such electronic format unless the submission is exempted or waived. In other words, such submissions must be consistent with the requirements set forth below.

A. Types of Submissions That Must Adhere to the Electronic Submission Requirement Described in This Guidance

Section 745A(a) of the FD&C Act applies to submissions under section 505(b), (i), or (j) of the FD&C Act and under section 351(a) or (k) of the Public Health Service (PHS) Act. These include the following submission types:

- Certain investigational new drug applications (INDs)[7,8]
- New drug applications (NDAs)
- Abbreviated new drug applications (ANDAs)
- Certain biologics license applications (BLAs)[9,10]

[7] This guidance is not applicable to investigational new drug applications (INDs) for devices that are regulated by CBER as biological products under section 351 of the PHS Act and that also require the submission of an IND before the submission of a biologics license applications (BLA). Although a discussion of which devices CBER regulates as biological products is outside the scope of this guidance, as a general matter, this category of INDs would include investigational devices that are used to screen blood donations for certain transfusion-transmissible infections and to test human cells, tissues, or cellular or tissue-based products to make a donor-eligibility determination. These submissions are subject to the requirements under section 745A(b) of the FD&C Act. See the guidance for industry and FDA staff *eCopy Program for Medical Device Submissions* (December 2015), which implements the electronic copy provisions of section 745A(b) for medical device submissions to FDA.

[8] This guidance is not applicable to noncommercial INDs.

[9] This guidance is not applicable to those devices that are regulated by CBER as biological products under section 351 of the PHS Act, including those that do not require the submission of an IND before the submission of a BLA. Although a discussion of which devices CBER regulates as biological products under section 351 of the PHS Act is outside the scope of this guidance, as a general matter, this category would include devices that are used to screen blood donations for certain transfusion-transmissible infections and reagents used in determining donor/recipient compatibility in transfusion medicine. These submissions are subject to the requirements under section 745A(b). See the guidance for industry and FDA staff *eCopy Program for Medical Device Submissions*.

[10] Specifically, this guidance is not applicable to submissions for blood and blood components, including Source Plasma.

Section 745A(a) also applies to all subsequent submissions, including amendments, supplements, and reports, to the submission types identified above.[11,12]

FDA considers master files to be submissions to an NDA, ANDA, BLA, or IND, and therefore to fall within the scope of requirements set forth in section 745A(a). These include new DMFs (21 CFR 314.420) and other master files relevant to a biological product (21 CFR 601.51)[13] and any amendments to or annual reports on previously submitted DMFs or other master files relevant to a biological product. This guidance also applies to submissions for drug/device combination products filed pursuant to section 505 of the FD&C Act or subsection (a) or (k) of section 351 of the PHS Act.

A submission that is not in the electronic format(s) described in this guidance will not be filed or received unless it has an exemption or waiver for the electronic submission requirements (see sections III.C., III.D., and III.E.) with respect to that submission.

Under section 745A(a)(3) of the FD&C Act, the electronic submission requirements do not apply to submissions described in section 561 of the FD&C Act (e.g., expanded access INDs and protocols for individual patients, including for emergency use; expanded access INDs and protocols for intermediate-sized patient populations; and expanded access treatment INDs and protocols). FDA will continue to accept submissions under section 561 in alternative formats (e.g., PDF files following the common technical document (CTD) organization).[14]

B. Timetable for Implementation of Electronic Submission Requirements

The requirement to submit NDAs, ANDAs, and BLAs electronically became effective 24 months after May 5, 2015 (i.e., May 5, 2017), the original date of finalization of this guidance (Revision 3). The requirement for INDs and master files, other than Type III DMFs, to be filed

[11] Although certain postmarketing safety report submissions fall within the scope of section 745A(a), FDA has separate regulations that require postmarketing safety reports to be submitted in electronic format (see 21 CFR 310.305, 314.80, 314.98. 600.80, and 600.81 and section 760 of the FD&C Act) and has issued related non-binding guidance on these postmarketing safety reports. Accordingly, FDA has not issued guidance under section 745A with respect to electronic format for postmarketing safety reports. For recommendations with respect to submissions related to postmarketing safety reports under §§ 310.305, 314.80, 314.98. 600.80, 600.81, or section 760 of the FD&C Act, see the draft guidance for industry *Providing Submissions in Electronic Format — Postmarketing Safety Reports* (June 2014). When finalized, this guidance will represent the FDA's current thinking on this topic. FDA may consider, at a future date, whether to include information pertaining to submission of postmarketing safety reports in electronic format in guidance under section 745A(a) of the FD&C Act.

[12] For further information about IND safety reports, see 21 CFR 312.32 and the guidance for industry *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012).

[13] For the purposes of this guidance, the term *DMF* refers to both drug master files and master files relevant to biological products.

[14] See the ICH guidance for industry *M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use* (October 2017).

electronically became effective 36 months after May 5, 2015 (i.e., May 5, 2018). For all of these submission types, if you do not have an exemption or waiver, you must electronically submit any amendments, supplements, and reports in eCTD format, even if the original submission was submitted to FDA in non-eCTD format before implementation of the electronic submission requirements.

The timetable for the initial implementation of the electronic submission requirement is shown in italics below. Table 1 summarizes the timetable.

> *On May 5, 2015, FDA issued the final guidance for industry on Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications. Submission types NDA, ANDA, and BLA must be submitted in eCTD format beginning May 5, 2017. IND submissions and master files, other than Type III DMFs, must be submitted in eCTD format beginning May 5, 2018.*

Table 1: Timetable for the Initial Implementation of the Electronic Submission Requirement

Submission Type	Final eCTD Guidance Posted on FDA Website (yyyy-mm-dd)	Date Requirement Begins (yyyy-mm-dd)
NDA ANDA BLA	2015-05-05	2017-05-05
Commercial IND Master Files Other Than Type III DMFs	2015-05-05	2018-05-05

Additional information regarding submissions pertaining to promotional materials made to the Office of Prescription Drug Promotion in CDER and to the Advertising and Promotional Labeling Branch in CBER is described in a separate guidance. Refer to that guidance for the timetable for implementation of those submissions in electronic format.[15]

[15] See the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format — Promotional Labeling and Advertising for Human Prescription Drugs* (April 2015). When finalized, this guidance will represent FDA's current thinking on this topic.

C. Types of Submissions Exempted From the eCTD Requirement Described in This Guidance

Section 745A(a)(2) of the FD&C Act allows FDA to establish exemptions from the electronic submission requirements. Accordingly, FDA has exempted the following from the eCTD requirements under section 745A(a)(2):[16]

1. All submissions to noncommercial INDs.[17] For the purposes of this guidance, the term *noncommercial product* refers to products that are not intended for commercial distribution; this exemption includes research and investigator-sponsored INDs.

2. All Type III DMF submissions.[18]

Although these specific submissions will be exempt from filing in eCTD format as described in this guidance, FDA still encourages applicants to send submissions in an alternative electronic format (e.g., PDF files following the CTD structure).[19]

D. Certain Positron Emission Tomography (PET) Drugs and Type II DMF Submissions That May Qualify for a Waiver From the eCTD Requirement Described in This Guidance

Section 745A(a)(2) authorizes FDA to establish criteria for waivers from its electronic submission requirements. Accordingly, FDA may grant a long-term waiver from the eCTD requirements under section 745A(a)(2)[20] in the following circumstances:

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[16] See section III.B of the 745A(a) Implementation Guidance (*Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act)*. Noncommercial IND submissions are not required to submit a request for this exemption.

[17] Noncommercial IND submissions are not required to submit a request for this exemption. Although INDs covered under section 561 of the FD&C Act might be referred to as a type of noncommercial IND, they have been statutorily excepted from the scope of section 745A(a). As a result, they need not submit in eCTD format, albeit for a different reason than the submissions exempted here. See section III.A of this guidance for information on the types of INDs covered under section 561 of the FD&C Act.

[18] Type III DMFs are submitted to the Agency to provide information regarding packaging or packaging materials in support of NDAs, ANDAs, or BLAs. The DMF web page is accessible at https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/drugmasterfilesdmfs/default.htm.

[19] If submission in eCTD format is not possible, FDA still encourages applicants to send submissions electronically in an alternative electronic format (e.g., PDF files following the common technical document (CTD) structure).

[20] See section III.C of the 745A(a) Implementation Guidance.

1. Certain Positron Emission Tomography (PET)[21] Drug Submissions

The requirement to comply with the eCTD requirement for certain PET IND, NDA, ANDA, or BLA submissions could adversely impact the development and availability of PET drugs. FDA may grant a waiver to a PET drug sponsor or applicant intending to submit an IND, NDA, ANDA, or BLA if *all* of the following apply:

(a) The applicant produces PET drugs at a single PET drug facility.

(b) PET drugs are the only FDA-regulated drug products (other than noncommercial drug or biologic products) manufactured or produced by the sponsor or applicant.

(c) The sponsor or applicant explains that, because it meets the criteria above, it cannot achieve compliance with eCTD requirements.

A waiver request should be sent to FDA before submitting the document(s) for which this waiver is claimed,[22] with an explanation regarding why the sponsor or applicant's compliance with the requirement cannot be achieved, including that the sponsor or applicant is representing that (a) through (c) above are met[23] and a description of the proposed alternative submission format[24] the sponsor or applicant will be using during the duration of the waiver (e.g., PDF files following the CTD structure).

The information provided in the waiver request may be verified through inspection or through a records request in lieu of an inspection.

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[21] PET is a medical imaging method that produces a computerized image (scan) using a unique type of radiopharmaceutical. A PET drug is a radioactive drug characterized by spontaneous disintegration of unstable nuclei by the emission of positrons and is used for providing dual photon positron emission tomographic diagnostic images (21 CFR 212.1). PET drugs are distinct among radiopharmaceuticals because of their unique production methods, and many are characterized by their short half-lives (some as short as 20 minutes). Many PET drug production facilities are close in proximity to the patients to whom the drugs are administered, and the production of the drug is on demand.

[22] Sponsors and applicants should request a pre-assigned application number before submitting a waiver request.

[23] See section 745A(a) of FD&C Act and 21 CFR 312.10 and 314.90(a)(1).

[24] See footnote 18.

2. Certain Type II DMF[25] Submissions

Holders of certain Type II DMFs that solely support an application for a PET drug or a noncommercial IND application may also qualify for a waiver. FDA recognizes that the holders of these Type II DMFs may be distinct from the holder of the application(s) in question. FDA may grant a waiver to a holder intending to submit a Type II DMF if the Type II DMF holder explains that it cannot achieve compliance with eCTD requirements because one of the following applies:

(a) The Type II DMF is intended to support an application for a PET drug (i.e., IND, NDA, ANDA, or BLA) and contains information regarding radiolabeled drug products or production of PET radionuclides, and the Type II DMF holder is an academic institution, government (state or federal) entity, or a non-profit[26] research organization.

OR

(b) The Type II DMF is solely used to support a noncommercial IND application, and the Type II DMF holder is an academic institution, government (state or federal) entity, or a non-profit research organization.

A waiver request should be sent to FDA before submitting the document(s) for which this waiver is claimed,[27] with an explanation regarding why the sponsor or applicant's compliance with the eCTD requirement cannot be achieved (i.e., that the sponsor or applicant is representing that (a) or (b) above is met), including a description of the proposed alternative submission format[28] the sponsor or applicant will be using during the duration of the waiver (e.g., PDF files following the CTD structure).

The information provided on the waiver request may be verified through inspection or through a records request in lieu of an inspection.

[25] Type II DMFs are submitted to the Agency to support drug applications to make quality information available for Agency evaluation of the quality of active pharmaceutical ingredients and drug products used in investigational studies.

[26] For the purposes of this guidance, a *non-profit* is a charitable organization recognized as a tax-exempt under section 501(c)(3) of the United States Internal Revenue Code of 1986 (Title 26 of the United States Code).

[27] Sponsors and applicants should request a pre-assigned application number before submitting a waiver request.

[28] See footnote 18.

3. Where to Submit Waiver Requests

The waiver requests for qualifying PET drugs or Type II DMFs should be submitted in one of the following ways:

- CDER:
  - Electronic Submission Gateway (ESG)[29]
  - Email to esub@fda.hhs.gov

- CBER
  - Email to ESUBPREP@cber.fda.gov

The waiver request should reference all products that are to be covered by the waiver. The waiver request should be clearly titled "**LONG-TERM WAIVER REQUEST — eCTD REQUIREMENTS**" in bold capital letters at the top of the first page of the submission.

4. FDA Response to Waiver Requests

FDA reviews waiver requests on a case-by-case basis.[30] FDA will generally respond to the requestor[31] in writing, stating whether the waiver is granted or denied and whether the proposed alternative submission format is acceptable. **Long-term waivers from the requirement to submit in eCTD format, if granted, will be valid for five (5) years from the date the waiver is granted, will apply only to the requestor, and will not be transferrable to another sponsor or applicant.** Sponsors or applicants may reapply to recertify their eligibility for this waiver up to 6 months before the waiver expiration date, using the same process as described in section III.D.3 of this guidance. If the criteria are no longer met at the time of recertification, the waiver will not be granted.

If FDA grants a waiver, the requestor should include a statement in the cover letter of each subsequent submission(s) indicating that an eCTD submission waiver has been granted by FDA, including the dates for the waiver.

Although these specific submissions may be exempt from filing in eCTD format as described in this guidance, FDA still encourages applicants to send submissions electronically in an alternative electronic format (e.g., PDF files following the CTD structure).[32]

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[29] Additional information concerning FDA's ESG is available at https://www.fda.gov/forindustry/electronicsubmissionsgateway/aboutesg/default.htm.

[30] The waiver request process will be in effect when the guidance is finalized.

[31] To follow up with the company, FDA will generally contact the individual who submitted the waiver request unless an alternate contact person is provided.

[32] See footnote 18.

E. Types of Submissions That May Qualify for a Short-Term Waiver From the eCTD Requirement Described in This Guidance

Section 745A(a)(2) of the FD&C Act authorizes the Agency to set forth criteria for waivers from the requirements of electronic submissions. FDA will grant short-term waivers from the eCTD requirement only in unique and rare circumstances and for a limited duration. Companies experiencing technical difficulties with transmission of their electronic submissions to FDA should consult FDA for technical assistance rather than submitting a waiver request. FDA may grant temporary waivers of the requirement for eCTD submission if one or more of the following events or circumstances exist:

- Extraordinary events or circumstances occur that are beyond the control of the submitter that justify a waiver, including but not limited to, natural disasters that impact computer operations.

- An unplanned long-term internet disruption or other unplanned event occurs that would preclude the sponsor from submitting in eCTD format (e.g., malware attacks).

- The sponsor or applicant intends to request a withdrawal of an application that has not yet converted to eCTD format.

- The sponsor or applicant submitted a request for withdrawal and has not yet received FDA's acknowledgement of the withdrawal.

1. Content of Waiver Requests

The sponsor or applicant's request to waive the eCTD electronic format requirement must include *all* of the following as supporting documentation to justify the waiver:[33]

(a) A description of the circumstances or event — including the anticipated duration of the circumstance or event — giving rise to the need for a waiver

(b) The requested duration of the waiver

(c) A description of the proposed alternative submission format[34] the sponsor or applicant will be using for the duration of the waiver

The request should reference all products that are to be covered by the waiver. The waiver request should be clearly titled "**WAIVER REQUEST — eCTD REQUIREMENTS**" in bold capital letters at the top of the first page of the submission.

[33] See 21 CFR 312.10(a)(3), and 314.90(a)(3).

[34] See footnote 18.

Please submit waiver requests before filing a submission to which the waiver is claimed.

2. Where to Submit Waiver Requests

Waiver requests for NDAs, BLAs, ANDAs, DMFs, and commercial INDs may be sent to FDA through the following means:

- CDER
  - Electronic Submission Gateway (ESG)
  - Email to esub@fda.hhs.gov

- CBER
  - Email to ESUBPREP@cber.fda.gov

3. FDA Response to Waiver Requests

FDA reviews waiver requests on a case-by-case basis. FDA will generally respond to the requestor[35] in writing, stating whether the waiver is granted or denied. If the waiver is granted, FDA will also generally include in its response letter a description of the alternate submission method(s) the Agency intends to accept and the time frame for the waiver. **Waivers of the requirement to submit in eCTD format, if granted, will be temporary, will apply only to the requestor, and will not be transferrable to another sponsor. If FDA grants a waiver, the requestor should include a statement in the cover letter of subsequent submission(s) indicating that an eCTD submission waiver has been granted by FDA, including the dates for the waiver.**

Although these specific submissions may be exempt from filing in eCTD format as described in this guidance, FDA still encourages applicants to send submissions electronically in an alternative electronic format (e.g., PDF files following the CTD structure[36]).

F. The eCTD Specifications

You must submit electronic submissions using the version of eCTD currently supported by FDA. The version of eCTD currently supported is specified in the Data Standards Catalog (available at https://www.fda.gov/media/85137/download) and is further described in the following technical specification documents:

- International Council for Harmonisation (ICH) *Electronic Common Technical Document Specification*

[35] To follow up with the company, FDA will generally contact the individual who submitted the waiver request unless an alternate contact person is provided.

[36] See footnote 18.

- ICH *eCTD Backbone File Specification for Study Tagging Files*

- FDA *eCTD Backbone Files Specification for Module 1*

Additional technical specification documents are cited throughout this document. For a complete listing of required technical supportive files (e.g., style sheets and valid values) that you will need to submit in the eCTD format, refer to the eCTD web page at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

G. Pre-Submission Considerations

Before making the first electronic submission to an application, you must obtain a pre-assigned application number by contacting the appropriate Center. Information regarding how to obtain a pre-assigned application number may be found on the eCTD web page at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

H. Submission Structure: Granularity, Files, and Folders

Document granularity, or the level for which the submission content is broken out into separate files, must be consistent with the *Granularity Document* found in the ICH guidance for industry *M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use* (October 2017) unless otherwise specified in the ICH M2 technical specification e*CTD IWG Question and Answer and Specification Change Request Document*.

With a few exceptions, the eCTD specification maps CTD headings to extensible markup language (XML) elements.[37] The specification indicates that each element (heading) is optional and that multiple document references (eCTD leaf elements) can be created under each heading.

You must also follow the FDA eCTD technical specification *The Comprehensive Table of Contents Headings and Hierarchy* for the comprehensive listing of headings and hierarchy and a section mapping the headings to their respective regulations. Because this is a comprehensive listing, not all headings are applicable to all submissions or submission types.

Files pertaining to each module must be placed in the appropriate folder (e.g., m1 – m5). The terms *folder* and *subfolder*, as used in this guidance, are intended to be synonymous with *directory* and *subdirectory*. The main submission, regional administrative folders, and certain subfolders must have specific names.

[37] For example, in Module 3, lower-level headings subordinate to 3.2.P.2 (e.g., 3.2.P.2.1, 3.2.P.2.1.1) are not mapped to an XML element. Consequently, leaf element files relating to, for example, 3.2.P.2.1, 3.2.P.2.1.1, either must be submitted as multiple leafs under the parent 3.2.P.2 element (heading) or combined into larger files and submitted at the 3.2.P.2 heading level.

You must use only letters, numbers, hyphens, or underscores in the folder and file names and not blank spaces or special characters. When naming folders and files, the length of the entire path must not exceed 150 characters. Empty folders and files must not be included in the submission.

All documents in the electronic submission must be placed in a main submission folder and named using a four-digit sequence number (which you must specify) that is unique within the application. The eCTD backbone file for modules 2 to 5 (*index.xml*) for the submission must be placed in this folder along with the checksum file for the eCTD backbone file (*index-md5.txt*).

Numbering for each subsequent submission to the same application is described in the FDA technical specification in section III.B of the *eCTD Backbone Files Specification for Module 1*. Sequence numbers are used to differentiate between submissions within the same application and need not correspond to the order in which they are received by FDA. It is not necessary for sequence numbers and IND serial numbers to match for submissions to an IND.

Subfolders within each module are required to organize files in a submission. These subfolders must be placed in the sequence number folder. Empty subfolders must not be included. The *util* subfolder is required to organize supporting eCTD technical files in the submission, as described in the ICH M2 technical specification *Electronic Common Technical Document Specification*. Other specific folder names that are compliant with the eCTD version 3.2.2 format can be found in the same document.

I. File Formats and Versions

Files within an eCTD submission must adhere to the formats and versions specified in the associated FDA technical specification *Specifications for File Format Types Using eCTD Specifications*. Portable Document Format (PDF) files submitted must adhere to the FDA technical specification *Portable Document Format (PDF) Specifications*.

J. Document Life Cycle

If a document replaces a document previously submitted with an eCTD backbone file within the same application, you must use the eCTD *replace* operation to indicate this, rather than submitting the file as *new*. You must not indicate that files are new if they are in fact replacing files already submitted. If you intend to remove a file, you must use the *delete* operation. For instructions, see the ICH M2 technical specification *Electronic Common Technical Document Specification*.

K. Summary of Clinical Efficacy and Summary of Clinical Safety

When submitting a Summary of Clinical Efficacy and/or Summary of Clinical Safety, the location of these documents within the eCTD must adhere to the FDA guidance for industry

Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (April 2009).

L. Datasets and Study Information

Datasets must only be provided in modules 3, 4, or 5 and not in modules 1 or 2. When providing study information in either module 4 or 5, you must include the Study Tagging File (STF) described in the associated ICH M2 technical specification *eCTD Backbone File Specification for Study Tagging Files* (see section III.F of this guidance). Datasets must be referenced in an STF using the appropriate STF *file-tag* describing the document's contents.

For further information regarding the submission of study data, see the FDA guidance for industry *Providing Regulatory Submissions in Electronic Format — Standardized Study Data* (December 2014).

M. Transmitting Electronic Submissions

The FDA ESG enables the secure submission of regulatory information for review and is our preferred method of transmission. For all submissions that are 10 gigabytes (GB) or smaller, you must use the FDA ESG.

For submissions that are greater than 10 GB, refer to the FDA technical specification *Transmitting Electronic Submissions Using eCTD Specifications*.

N. FDA Forms

Electronic submissions must include only FDA fillable forms (e.g., Form FDA 1571 or Form FDA 356h) and electronic signatures to enable automated processing of the submission. The FDA forms are available at https://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm. Scanned images of FDA forms will not be accepted.

O. Restrictions on Submission of Paper Copies

When submitting in eCTD format, paper copies of the application, including review copies and desk copies in paper, must not be submitted. The only exception to this is the submission of paper copies of meeting briefing materials, when requested, as described in the FDA guidances for industry on formal meetings between the FDA and sponsors or applicants.[38]

[38] See also the following draft guidances: *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017) and *Formal Meetings Between the FDA and Sponsors or Applicants of BSUFA Products* (June 2018). When finalized, these guidances will represent FDA's current thinking on this topic.

P. Receipt Date

The receipt date for an electronic submission will be determined only after the submission has passed a technical validation check to ensure that it can be opened, processed, and archived. The submitter is responsible for monitoring their receipt pathway to determine whether a submission has been rejected. Additional information on the validation of electronic submissions is available in the FDA technical specification *Specifications for eCTD Validation Criteria*.

Additional information on receipt dates for electronic submissions is available in the FDA guidance for industry *Providing Regulatory Submissions in Electronic Format — Receipt Dates* (February 2014).

Contact Information

For questions related to providing electronic submissions according to the recommendations in this guidance, you should contact the Center electronic submission coordinator at esub@fda.hhs.gov for submissions to CDER and at esubprep@fda.hhs.gov for submissions to CBER. Specific questions pertaining to the content of applications should be directed to the appropriate review division or office.

TECHNICAL SPECIFICATION DOCUMENTS REFERENCED IN THIS GUIDANCE

The following are technical specification documents referenced in this guidance (see section I). Documents are listed in order of first appearance in this guidance.

For a complete listing of the current technical supportive files that you will need in order to submit in eCTD format, refer to the *eCTD Submission Standards* document located on the eCTD web page at https://www.fda.gov/ectd.

1. ICH M2 technical specification, *Electronic Common Technical Document Specification*

2. ICH M2 technical specification, *The eCTD Backbone File Specification for Study Tagging Files*

3. FDA technical specification, *eCTD Backbone Files Specification for Module 1*

4. ICH M2 technical specification, *eCTD IWG Question and Answer and Specification Change Request Document*

5. FDA technical specification, FDA eCTD *Comprehensive Table of Contents Headings and Hierarchy*

6. FDA technical specification, *Specifications for File Format Types Using eCTD Specifications*

7. FDA technical specification, *Portable Document Format (PDF) Specifications*

8. FDA technical specification, Transmission Specifications, *Transmitting Electronic Submissions Using eCTD Specifications*

9. FDA technical specification, eCTD Validation Specifications web page, *Specifications for eCTD Validation Criteria*

RELATED REFERENCES

The guidance documents referenced below can be accessed via FDA's guidance web page at https://www.fda.gov/industry/fda-basics-industry/guidances.

1. FDA guidance for industry *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* (December 2014)

2. FDA guidance for industry *Providing Regulatory Submissions in Electronic Format — Standardized Study Data* (December 2014)

3. FDA draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017)

4. FDA draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BSUFA Products* (June 2018)

5. FDA draft guidance for industry *Providing Submissions in Electronic Format – Postmarketing Safety Reports* (June 2014)

6. FDA guidance for industry *Providing Regulatory Submissions in Electronic Format — Receipt Dates* (February 2014)

7. ICH guidance for industry *M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use* (October 2017)

8. FDA guidance for industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* (April 2009)