Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Receipt Date

DRAFT GUIDANCE

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Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Gary Gensinger at 301-796-0589, or (CBER) Michael Fauntleroy at 301-827-5132.

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)

June 2007
Electronic Submissions

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U.S. Department of Health and Human Services
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This is one in a series of guidance documents intended to assist sponsors and applicants making regulatory submissions to the Food and Drug Administration (FDA) in electronic format. This guidance provides information on what the FDA will consider to be the receipt date for submissions provided in electronic format to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). This guidance applies to submissions of investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), and master files (MFs) in electronic format, including original submissions, amendments, supplements, and all other regulatory submissions to these applications. The guidance applies to any of these regulatory submissions that contain information in an electronic format, including hybrid submissions (i.e., mixed electronic and paper submissions sent in the same package to the appropriate, designated document room at the FDA). This guidance is not limited to those submissions provided in the electronic common technical document (eCTD) format.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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

II. BACKGROUND

When the FDA receives a submission, the receipt date is used to determine important regulatory milestones. For example, the receipt date of an IND establishes the FDA's 30-day safety review cycle for the application. Clinical investigations cannot begin during this 30-day time period, unless the FDA notifies the sponsor that it may start its investigations earlier (see 21 CFR 312.40). Similarly, for an NDA or BLA, the receipt date determines the review performance goal date according to the Prescription Drug User Fee Act (PDUFA) goals letter.[2] For a submission entirely in a paper format, or a hybrid submission, the FDA determines the official receipt date to be the date the submission arrived at the appropriate, designated document room. For a submission entirely in an electronic format, the FDA has determined the official receipt date to be the date the submission arrived at the appropriate, designated document room (e.g., submission on a CD-ROM) or into the electronic submission gateway (ESG). We consider a submission that arrives in two parts (e.g., one in a paper format and the other in an electronic format into the ESG or on a CD-ROM sent to the appropriate, designated document room in a separate package) to be two separate submissions and the receipt date for each is determined individually. For submissions that arrive in two parts, the official receipt date for the NDA and BLA review performance goals has been the receipt date of the part that arrives at the FDA first. The part that arrives at the FDA later is considered an amendment.

Occasionally, a submission that is provided in an electronic format may have technical deficiencies that prevent us from opening, processing, and/or archiving the submission. Examples of such deficiencies include:

- Defect in the media (e.g., CD-ROMs)
- Failure to provide an electronically readable 356h or 1571 form for submissions sent to the FDA through the ESG
- Providing an eCTD submission using a *sequence number* that was submitted previously
- Failure to provide the index.xml and us-regional.xml files required for an eCTD submission
- Presence of a virus
- File format incompatibility

When such technical deficiencies occur, FDA review of the submission cannot begin until the technical deficiencies are corrected.

Submissions provided in an electronic format that cannot be reviewed by the FDA because of technical deficiencies may interfere with the FDA's assessment of the submissions. For IND submissions, the time needed to correct the technical deficiencies can leave FDA reviewers with

[2] See http://www.fda.gov/oc/pdufa/PDUFAIIIGoals.html.

inadequate time to assess the risks of the proposed investigations during the 30-day period before clinical investigations can begin. For NDAs or BLAs, such technical deficiencies have caused the FDA to be unable to commence our review promptly. This in turn has made management of the review process and meeting the PDUFA goals even more difficult, made scheduling of advisory committees harder, and generally has interfered with a tightly scheduled process.

On occasion, such technical deficiencies have resulted in the issuance of refuse-to-file actions. However, this is not the best solution because a refuse-to-file decision is not made until 60 days after the application is submitted. Furthermore, refusals to file also can lead to forfeiture of a portion of user fees by the applicant.[3] It is in everyone's interest to correct technical deficiencies associated with an electronic submission expeditiously, so that the submission can be reviewed promptly.

To encourage sponsors to ensure that electronic submissions are free of technical deficiencies that can delay FDA review of the submission, the FDA is changing its policy on the receipt date for submissions provided in an electronic format.

III. POLICY

The FDA will consider a technically deficient application *not received* until the technical deficiencies are resolved and the application is resubmitted in a format that we can process, review, and archive. On rare occasions, however, the FDA may still refuse to file a technically deficient marketing application (see examples #5 and #7 in Appendix A).

The receipt date for a submission in an electronic format will be determined only after the submission has passed a technical validation check to ensure that it can be opened, processed, and archived. The FDA will post technical specifications that describe the validation checks that will be performed on each type of submission in electronic format (e.g., INDs, NDAs, BLAs).[4]

If a submission passes technical validation, then the receipt date will be the business day on which the submission arrived at the appropriate, designated document room or into the ESG. If, however, the submission fails the technical validation check, it will not be considered received until after the technical deficiencies are corrected. The FDA will notify the sponsor or applicant of the technical deficiencies and ask that they be corrected before resubmission. The validation check process will be repeated when the material is resubmitted. See Appendix A for examples on how the receipt date policy will be applied depending on the submission scenario. For hybrid submissions, the receipt date will be determined only after the electronic portion has passed technical validation (see example #4 in Appendix A).

[3] Applicants whose applications are refused for filing are refunded 75 percent of the user fee under section 736(a)(1)(D) of the Federal Food, Drug, and Cosmetic Act. The 25 percent of the user fee that is retained is not credited toward the subsequent resubmission, which is subject to the full user fee.

[4] See http://www.fda.gov/cder/regulatory/ersr.

We encourage sponsors and applicants who are inexperienced with submitting applications in an electronic format to obtain technical assistance before submitting an application. Assistance is available by contacting esub@fda.hhs.gov (CDER) or esubprep@fda.hhs.gov (CBER).

APPENDIX A: EXAMPLES OF DETERMINING RECEIPT DATE

The following examples illustrate how the FDA will determine the receipt date of submissions provided in electronic format depending on the submission scenario.

1. **All electronic IND —** An IND in eCTD format arrives on October 1 via the ESG. The submission passes technical validation on October 2. The receipt date will be October 1, the date the submission was received.

2. **All electronic amendment to an IND —** A special protocol assessment (SPA) for an IND arrives on October 1 on a CD-ROM. After loading, it is determined that a critical document is corrupt. The sponsor submits a replacement document on October 4, which is loaded and determined accessible. The receipt date for the SPA will be October 4.

3. **All electronic BLA —** A BLA in eCTD format arrives on October 1 via the ESG. The index.xml file, a necessary component of the eCTD, is missing; therefore, the submission fails technical validation. The FDA notifies the applicant that the submission failed the technical validation check and requests a corrected replacement eCTD. The applicant submits a corrected replacement eCTD on October 4. The corrected replacement eCTD passes technical validation on October 5. The receipt date will be the arrival date of the corrected replacement eCTD, October 4.

4. **Hybrid NDA —** An NDA containing 100 volumes in a paper format and datasets and labeling in an electronic format on a CD-ROM arrives on October 1. The CD-ROM contains certain datasets in an incompatible file format; therefore, the submission fails technical validation. The FDA notifies the applicant that the submission failed the technical validation check and requests a corrected replacement CD-ROM. The applicant has difficulty reliably converting the files to an appropriate file format, which delays the arrival of the corrected replacement CD-ROM to December 3. The corrected replacement CD-ROM passes technical validation. The receipt date for the hybrid submission will be December 3.

5. **NDA in a paper format with an electronic amendment —** An NDA containing 100 volumes in a paper format arrives on October 1. The FDA considers it a paper-only submission and the receipt date would be October 1. However, the application is actually incomplete and an amendment containing datasets and labeling in an electronic format on a CD-ROM arrives on October 15. The CD-ROM contains certain datasets in an incompatible file format; therefore, the amendment fails technical validation. The FDA notifies the applicant that the amendment failed the technical validation check and requests a corrected replacement CD-ROM. The applicant has difficulty reliably converting the files to an appropriate file format and the corrected replacement CD-ROM does not arrive at the FDA in sufficient time to permit completion of the filing review. The application will be considered incomplete and the FDA will issue a refuse-to-file action.

This example illustrates the risk of providing the FDA with an incomplete application in the original submission. Had the CD-ROM arrived with the paper portion, the submission would have been a hybrid NDA and the applicant could have avoided a refuse-to-file action, as illustrated in example #4. It should be noted that the FDA is not obligated to review unsolicited amendments during the current review cycle, so applicants risk a refuse-to-file action in this scenario, even if the amendment passes technical validation, because the paper portion of the NDA was incomplete (see the guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products*).[5]

6. **All electronic BLA with a paper amendment —** A BLA in electronic format arrives on October 1 via the ESG. It passes technical validation on October 2. The receipt date would be October 1. However, the application is actually incomplete and an amendment to the BLA in a paper format arrives on October 15. The FDA chooses to review the unsolicited amendment and has sufficient time to permit completion of the filing review. The receipt date for the BLA will be October 1 as originally determined and the receipt date for the amendment will be its arrival date, October 15. It should be noted that because the FDA is not obligated to review an unsolicited amendment during the current review cycle, and without that amendment the application is incomplete, the incomplete application could have been subject to a refuse-to-file action.

7. **All electronic NDA —** An NDA in eCTD format arrives on October 1 on two CD-ROMs. It passes technical validation on October 2. The receipt date would be the arrival date, October 1. During the filing review, the clinical reviewer notes that all 12 clinical study reports appear under one single incorrect heading, and all the subsections of the study reports are mixed up, making it impossible to determine which subsections correspond with which report. Therefore, the clinical section of the application is impossible to review. This technical error in assembling the eCTD was missed by the automated validation steps performed upon arrival of the CD-ROMs because it can be detected only by a manual review of the content of the NDA. The applicant is unable to correct the technical deficiency in sufficient time to permit completion of the filing review and the FDA will issue a refuse-to-file action.

[5] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.