# Guidance for Industry

## Providing Regulatory Submissions in Electronic Format — Receipt Dates

**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)**

**February 2014**
**Electronic Submissions**

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*Contains Nonbinding Recommendations*

# Guidance for Industry[1] Providing Regulatory Submissions in Electronic Format — Receipt Dates

This guidance represents 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, applicants, and others making regulatory submissions to the Food and Drug Administration (FDA) in electronic format.

This guidance explains how FDA will assign receipt dates to regulatory submissions to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) for drug products.[2] Although the guidance does not address receipt dates for citizen petitions, it applies to all of the following submission types:

- Investigational new drug applications (INDs)
- Premarket approval applications for drugs, including new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), and amendments and supplements to these applications
- Master files (MFs)
- Postapproval studies (whether submitted as supplements to approved applications or otherwise)
- Submissions related to products marketed without an approved application

[1] 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.

[2] For purposes of this guidance, unless otherwise specified, references to "drugs" and "drug products" include drugs approved under the FD&C Act and biological products licensed under the PHS Act, other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)). While CBER reviews some device submissions, this guidance does not apply to submissions related to devices.

- Adverse event reports
- Original submissions, amendments, supplements, postmarket reports, and all other regulatory submissions to these applications.

The guidance applies to these regulatory submissions if they contain information in either electronic or paper format, including hybrid submissions (i.e., mixed electronic and paper submissions sent in the same package to the appropriate receiving unit at FDA). This guidance is not limited to those submissions made using the electronic common technical document (eCTD) format.

Any provisions of FDA's regulations that describe how receipt dates or submission dates are determined for a particular type of submission take priority over this guidance.

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.

## II. BACKGROUND

When FDA receives a submission, the submission is assigned a receipt date. This date may be used to determine important regulatory milestones. For example, the receipt date of an IND establishes FDA's 30-day safety review cycle for the application. Clinical investigations cannot begin during this 30-day time period, unless FDA notifies the sponsor that investigations may start earlier.[3] Similarly, for a premarket approval application, such as an NDA, BLA, ANDA, or a supplement to an approved application, the receipt date determines the review performance goal date established under the applicable user fee legislation.[4] It is important to recognize, however, that the "receipt date" as defined under this guidance may, as explained below, differ from the date of "submission" of an ANDA. It is also important to distinguish, as explained further below, the "receipt date" as defined under this guidance from the decision by FDA whether or not an ANDA will be "received" within the meaning of the statute and FDA regulations.

For certain postmarket submissions, the receipt date is used to help determine compliance with regulatory time frames. For example, the receipt date for a postmarket study submission will determine whether the submission was received in accordance with the postmarket study requirements; the receipt date for a serious, unexpected postmarket adverse event report submission will determine whether the submission was received within the required 15 calendar day timeframe.

[3] See 21 CFR 312.40.

[4] The Prescription Drug User Fee Act (PDUFA), the Generic Drug User Fee Amendments (GDUFA), or the Biosimilar User Fee Act (BsUFA).

### A. Regulatory Distinction Between Submission and Receipt

In some situations, the statute or regulations assign significance to the date on which an ANDA is *submitted*. For example, the date on which a substantially complete ANDA is submitted may determine whether or not that ANDA earns 180-day exclusivity vis-à-vis other ANDAs. As stated in the guidance *180-Day Exclusivity When Multiple ANDAs Are Submitted on the Same Day,* FDA applies a multiple first applicant approach to eligibility for 180-day exclusivity by considering all substantially complete ANDAs, amendments, and supplements containing a paragraph IV certification to a listed patent that are submitted on the same day as being first applicants when no paragraph IV certification to the patent has been submitted on any previous day, as long as the applications comply with the applicable requirements for submission. [5]

The Generic Drug User Fee Amendments of 2012 (GDUFA) include a provision regarding the date of submission for Type II drug master files and abbreviated new drug applications (ANDAs), including amendments and supplements to ANDAs. Under this provision, these submissions are deemed to be *submitted* to FDA on the day when transmission to the electronic submission gateway (ESG) is completed, except when such a submission arrives on a weekend, federal holiday, or day when the FDA office that will review the submission is otherwise not open for business. In that case, the submission is deemed to be submitted on the next day when that office is open for business. GDUFA further states that if such a submission arrives in physical media form, it is deemed to be submitted on the day it arrives at FDA's appropriate designated document room.[6] As explained further below, there may be a short lag time between the completion of the submission of an ANDA to the ESG and completion of the transmission from the ESG to the appropriate Center and production of the corresponding Official Center Acknowledgement. In rare circumstances (when completion of the submission to the ESG fell at the very end of one day and the transmission of the corresponding Official Center Acknowledgment occurred at the beginning of the next day), that could mean that the date of submission would be different from the date of receipt.

### B. Decisions to *Receive* or *File* an Application for Review

FDA regulations set forth criteria for the receipt and initial review of NDAs, BLAs, and ANDAs to determine whether they may be *filed* (in the case of NDAs and BLAs) or *received* (in the case of ANDAs) and placed into review.[7] The decision whether or not the NDA may be filed or the ANDA may be received depends both on whether appropriate fees have been paid and whether the applications are found to be adequate for review. The *receipt date* for a premarket application, as described in this guidance, is the date on which an application is deemed to have arrived at FDA. It should not be confused with our subsequent decision to *file* an NDA or a BLA for review or to *receive* an ANDA for review.

[5] See also 21 CFR 314.107(c)(1) and section 505(j)(5)(D)(i)(I)(aa)(BB) of the Federal Food, Drug, and Cosmetic Act (making the *date of submission* an issue with respect to forfeiture of 180-day exclusivity).
[6] See FD&C Act, section 744B(a)(5).
[7] See 21 CFR 314.101 and 601.2.

## III. POLICY

### A. Receipt Date

For the purpose of assigning receipt dates, if an electronic submission covered in this guidance arrives via the ESG Monday through Friday, it is deemed to have arrived at FDA on the date and time corresponding to the Official Center Acknowledgment (second acknowledgment) that is automatically sent to the submitter by the ESG.[8] However, except as described under heading C below, if such a submission arrives through the ESG on a weekend, a federal holiday, or another day on which the FDA office that will review the submission is not open for business, it is deemed to have arrived at FDA on the next day when that office is open for business. If a submission covered in this guidance is submitted in physical media (e.g., paper or CD-ROM), it is deemed to have arrived at FDA on the date on which it arrived physically at the appropriate receiving unit, while open for business, for the FDA center that will review the submission.

The hours during which FDA can receive a submission – for the purpose of assigning a receipt date – are summarized in the following table.[9]

| Delivery Method | Hours for Receipt of Submission | |
|---|---|---|
| Postal Service or Private or Commercial Courier | CDER | 7:00 AM through 6:00 PM |
| | CBER | 8:00 AM through 4:30 PM |
| ESG | Monday through Friday 12:00 AM to 11:59 PM,[10] excluding federal holidays and days when the FDA office that will review the submission is closed | |

### B. Submission Date

When an application is submitted electronically, the submission and receipt occur at almost the same time. In rare instances, however, an application submitted electronically may be submitted shortly before midnight and received shortly after midnight. As referenced above, GDUFA states that certain types of submissions (i.e., Type II drug master files, ANDAs, and amendments and supplements to ANDAs) are deemed to be *submitted* to FDA on the day when transmission to the ESG is completed. This occurs slightly sooner than the Official Center Acknowledgment

[8] Additional information on ESG acknowledgements can be found on FDA's website (Electronic Submissions Gateway - Frequently Asked Questions).

[9] The unusual situation of a lapse of appropriations requires a special explanation. In some circumstances, as in October 2013, some FDA functions may continue during a lapse in appropriations because funding is available from user fees that were collected in the previous fiscal year but not yet expended. During a lapse in appropriations, however, FDA cannot accept new applications for which required user fees were not paid prior to the lapse in appropriations. This means that, for purposes of receipt of such new applications, the government is considered not to be open for business during a lapse in appropriations. For that reason, even if document rooms are open during the lapse period, those rooms will not be considered to have received physical submissions of such new applications during that period. Similarly, for ESG submissions, new applications for which required user fees were not paid prior to the lapse in appropriations will not be received until the lapse ends (i.e., the FDA office that will review the submissions will not be considered to be open for business during the lapse period).

[10] All times referred to in this guidance are Eastern Standard Time/Eastern Daylight Time.

(the ESG's second acknowledgment), which is used to determine the date of receipt. For ANDAs and Type II drug master files, the date of submission is determined in accordance with GDUFA (i.e., the date on which transmission to the ESG was completed).

For most submissions, the distinction between submission and receipt will have no significance. In rare instances, however, the date of submission thus determined may differ from the date of receipt, and certain significance may attach to the date of submission (see examples 1.k and 1.l in the Appendix to this guidance).

### C. When Reporting Deadlines are Established in Terms of Calendar Days

FDA regulations require that some information be reported to FDA within a certain number of calendar days. For example, 21 CFR 314.80 requires applicants to report each adverse drug experience that is both serious and unexpected as soon as possible and no later than 15 calendar days of initial receipt of the information by the applicant. Whenever information must be reported to FDA by a deadline established as calendar days and the report is submitted electronically through the ESG, the information will be deemed to have arrived at FDA on the date and time corresponding to the Official Center Acknowledgment (second acknowledgment) that is automatically sent to the submitter by the ESG, whether that occurs on a weekday, weekend, federal holiday, or other day on which the FDA office reviewing the information is not open for business.

### D. Deficiencies

Occasionally, a submission that is provided in electronic format may have technical deficiencies that prevent FDA from processing, reviewing, and archiving the submission. Examples of such deficiencies include, but are not limited to:

- Damaged media (e.g., unreadable CD-ROM)
- Failure to provide an electronically readable and valid FDA Form or submission (e.g., Form FDA 1571, Form FDA 356h), sent to FDA through the ESG
- Failure to provide a properly formatted and electronically readable CD
- Providing an electronic common technical document (eCTD) submission without the required index.xml and us-regional.xml files or using a *sequence number* that was submitted previously[11]
- Presence of a computer virus
- File format incompatibility
- Incorrect or inaccurate metadata, such as application type or number
- Providing an incomplete submission form that will not pass an internal technical validation for mandatory fields of metadata
- Incorrect or missing filename extensions that specify the file types

[11] See the eCTD Validation Specifications on the FDA website

When such technical deficiencies occur, FDA's processing of the submission cannot begin until the technical deficiencies are corrected. FDA considers a technically deficient electronic submission to be ***not received*** (i.e., not present at FDA and not under review) until all technical deficiencies are resolved and the submission is in a format that we can process, review, and archive. Therefore, it is in the interest of applicants to prevent or identify and expeditiously correct technical deficiencies associated with an electronic submission, so that the submission can be processed and reviewed promptly and receipt dates and times can be set efficiently.

The following describes the potential effects of technical deficiencies in a submission:

- The receipt date of an electronic submission is established tentatively when the submission arrives through the ESG and then established permanently when the submission is determined to be technically acceptable. FDA posts technical information that describes the validation checks that FDA performs on each type of submission in electronic format (e.g., INDs, NDAs, BLAs).[12]
- FDA notifies the submitter of any technical deficiencies and asks that these be corrected as each difficulty is encountered. It may not be possible to discover all technical difficulties at once. For example, some problems, such as an unreadable CD-ROM, prevent the discovery of further problems within the content of a submission; those would be communicated at a later date.
- FDA determines the official receipt date to be the date a non-deficient submission, *or resubmission*, arrives at the appropriate designated receiving unit.

If technical deficiencies in a premarket approval application are not resolved before the start of a new fiscal year (October 1), the user fee associated with the submission may be adjusted. This would occur when there are changes to user fees at the beginning of the fiscal year.

[12] Certain validation information, including the eCTD Validation Specifications, is posted on the FDA website, under "Electronic Submissions to CDER."

## APPENDIX: EXAMPLES OF DETERMINING RECEIPT DATE

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

### 1. All-electronic submissions, e.g., INDs, IDEs, BLAs, NDAs, ANDAs

a. An IND 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.

b. An IND in eCTD format arrives on March 3 via the ESG and is received by FDA's Center for Devices and Radiological Health (CDRH). The submission has been directed to the incorrect receiving unit. The submitter is notified of the error and is asked to resubmit the submission to the proper receiving unit. The sponsor corrects its error, and the IND submission is received at CDER on March 4 and passes technical validation. The receipt date will be March 4, the date the submission was received at the proper receiving unit.

c. An amendment to an IND — a special protocol assessment (SPA) — arrives on October 1 on a CD-ROM and, after loading, it is determined that a critical document is corrupt. FDA notifies the sponsor, and the sponsor submits a replacement document on October 4; it is loaded and determined accessible. The receipt date for the SPA will be October 4.

d. 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. 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.

e. An ANDA in eCTD format arrives on October 1 via the ESG. The submission fails technical validation. 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 at noon on October 4. The corrected replacement eCTD passes technical validation on October 5. The date of submission of the ANDA is the arrival date of the corrected replacement eCTD, October 4. Whether the ANDA is *received* for review within the meaning of 21 CFR 314.101(b) is determined in accordance with that regulation.

f. An applicant submits an adverse event individual case safety report (ICSR) for an NDA product via the ESG on October 1.[13] The submission passes through the ESG to the receiving unit, but cannot be loaded into the appropriate FDA safety database due to

[13] FDA determines the receipt date for adverse event reports based on the date the submission reaches the receiving unit's inbound folder. The ESG sends a first acknowledgment, and assuming that the report is successfully received by the inbound folder, a second acknowledgment is sent and used as the official center receipt date.

errors in the incoming submission. The reporter receives an acknowledgement from the system indicating the errors that prevented the submission from loading successfully. The reporter corrects the errors and submits the corrected submission via the ESG on October 3. The submission passes through the ESG to the receiving unit and successfully loads into the appropriate FDA safety database on October 4. The receipt date will be the arrival date of the corrected submission to the receiving unit, October 3.

g. A licensed manufacturer submits an adverse event ICSR for a BLA product via the ESG on October 1. The submission passes through the ESG to the receiving unit, but the target FDA safety database is unavailable due to a planned system outage for maintenance. The database becomes available again on October 3, and the report is processed and loaded into the database at that time. The receipt date will be the arrival date of the report to the receiving unit, October 1.

h. A manufacturer submits an adverse event ICSR for a prescription product without an approved application via the ESG on October 1. Due to a technical problem FDA is having with the ESG, the report is not received by the ESG or the receiving unit, so the receipt date is not set. The manufacturer is informed of the problem on October 3 and resubmits the report that day. The report is now successfully received by FDA, via the ESG, which sets the receipt date as October 3. Because the delay was the result of an FDA problem, FDA re-sets the receipt date to October 1.

i. An NDA in eCTD format arrives on September 29 on two CD-ROMs. It fails technical validation due to a damaged CD-ROM. The applicant is notified and resubmits new CD-ROMs. The new CD-ROMs are received at FDA on October 4 and pass technical validation. Because the application is received on October 4, the next fiscal year, the user fee will be assessed at the new fee amount, and the applicant will be required to submit the appropriate user fee payment.

j. An applicant submits an NDA via the ESG at 8:30 pm Pacific Standard Time on June 1. This corresponds to 11:30 pm Eastern Standard Time (EST). Arrival of the NDA through the ESG is not complete until 12:01 am EST on June 2. If it passes technical validation, the NDA will be assigned a receipt date of June 2.

k. Three substantially complete ANDAs are sent to FDA electronically on April 20, all relying on the same reference listed drug and all containing *paragraph IV* certifications challenging a patent for the reference listed drug. No applicant has previously challenged the patent. Of these three ANDAs, the last to arrive is transmitted *to* the ESG and that transmission is completed at 11:55 pm EST, but that ANDA does not completely arrive at CDER until 12:01 am EST the next day, April 21, according to the second acknowledgment automatically generated by the ESG. Assuming they pass technical validation, the first two ANDAs will be assigned a receipt date of April 20, and the third will be assigned a receipt date of April 21. In accordance with GDUFA, however, all three ANDAs will be assigned a submission date of April 20 because the transmission of all three *to* the ESG was completed on April 20. Consistent with the guidance *180-Day Exclusivity When Multiple ANDAs are Submitted on the Same Day*, all three applicants

are regarded as *first applicants* and may be eligible for shared 180-day generic drug exclusivity. Applicants in this situation are encouraged to make their submissions with time to spare, taking into account possible unexpected delays in transmission time to the ESG.

l. As in the last example, three substantially complete ANDAs are sent to FDA electronically on April 20, all relying on the same reference listed drug and all containing *paragraph IV* certifications challenging a patent for the reference listed drug. No applicant has previously challenged the patent. The third applicant begins transmission to the ESG at 11:55 pm EST on April 20. Due to a slow connection, transmission *to* the ESG is not completed until 12:05 am April 21. Assuming they pass technical validation, the first two ANDAs will be assigned a receipt date of April 20, and the third will be assigned a receipt date of April 21 (receipt dates corresponding to the ESG's second acknowledgment). In accordance with GDUFA, the first two ANDAs will be assigned a submission date of April 20, and the third will be assigned a submission date of April 21, the date on which transmission to the ESG was completed. Consistent with the guidance *180-Day Exclusivity When Multiple ANDAs are Submitted on the Same Day*, the first two applicants are regarded as *first applicants* and may be eligible for shared 180-day generic drug exclusivity. The third is not.

m. An applicant submits an NDA via the ESG at noon on June 1. The applicable user fee for the application is not paid until June 10. FDA will adjust the receipt date for the NDA to June 10. (This applies to physical as well as electronic submissions.)

n. An applicant submits an ANDA via the ESG at noon on June 1. The applicable user fee for the application is not paid until June 30. FDA will adjust the receipt date for the ANDA to June 30. (This applies to physical as well as electronic submissions.) In addition, because the fee was paid more than 20 days after it was due, by statute FDA must consider the ANDA not to have been "received" until June 30.[14]

## 2. Hybrid (or mixed) submissions (electronic and paper)

a. A hybrid 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. 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 November 15. The corrected replacement CD-ROM passes technical validation. The receipt date for the complete mixed submission will be November 15.

[14] FDCA Section 744B(g)(3). Moreover, the ANDA will not be considered to be "substantially complete" when submitted, and can only be considered to be "substantially complete" as of the date the fee is paid, FDCA Section 744B(n), a fact that can have important implications for claims of 180-day exclusivity.

b. 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. FDA chooses to review the amendment and has sufficient time to permit completion of the filing review. The receipt date for the BLA is October 1 as originally determined, and the receipt date for the amendment is its arrival date, October 15. In this case, the receipt date for the review performance goal is October 1.