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[Docket No. FDA-2004-N-0510] (formerly Docket No. 2004N-0267)

Applications for Approval to Market a New Drug; Complete Response  
Letter; Amendments to Unapproved Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations on new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for approval to market new drugs and generic drugs (drugs for which approval is sought in an ANDA). The final rule discontinues FDA's use of approvable letters and not approvable letters when taking action on marketing applications. Instead, we will send applicants a complete response letter to indicate that the review cycle for an application is complete and that the application is not ready for approval. We are also revising the regulations on extending the review cycle due to the submission of an amendment to an unapproved application and starting a new review cycle after the resubmission of an application following receipt of a complete response letter. In addition, we are adding to the regulations on biologics license applications (BLAs) provisions on the issuance of complete response letters to BLA applicants. We are

taking these actions to implement the user fee performance goals referenced in the Prescription Drug User Fee Amendments of 2002 (PDUFA III) that address procedures and establish target timeframes for reviewing human drug applications.

DATES: This rule is effective [insert date 30 days after date of publication in the FEDERAL REGISTER].

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## I. Background

In the Federal Register of July 20, 2004 (69 FR 43351), we published a proposed rule to replace approvable and not approvable letters with complete response letters and to make other changes to our regulations on NDAs, ANDAs, and BLAs. Previous § 314.110 (21 CFR 314.110) set forth provisions on the issuance of and response to approvable letters; § 314.120 (21 CFR 314.120) addressed the issuance of and response to not approvable letters. The proposed rule proposed to replace those provisions with a revised § 314.110 regarding the issuance of complete response letters upon completion of our review of NDAs and ANDAs.

### A. The Proposed Rule

The preamble to the proposed rule stated that the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) agreed to revise their regulations and procedures to provide for the issuance of complete response letters as part of our prescription drug user fee performance goals. We first made the commitment regarding complete response letters as part of the user fee performance goals established in conjunction with the enactment of the Food and Drug Administration Modernization Act of 1997 (Public Law 105-115) (the user fee provisions of this act are known as "PDUFA II"). We repeated this commitment in the performance goals developed in conjunction with the enactment of the Prescription Drug User Fee

Amendments of 2002 (PDUFA III), set forth in title V, subtitle A, of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Public Law 107-188). Section 502 of PDUFA III states that user fees will be dedicated to expediting the drug development process and the process for review of human drug applications in accordance with the new performance goals, which are set forth in an enclosure to letters from Tommy Thompson, Secretary of Health and Human Services, to the Chairman of the House Committee on Energy and Commerce and the Ranking Member of the Senate Committee on Health, Education, Labor, and Pensions (June 4, 2002) (Goals Letter).

The proposed rule stated that, because there are no provisions on action letters in the biological product regulations, CBER had only to change its standard operating procedures to incorporate the issuance of a complete response letter at the end of a review cycle for a biological product. We noted that although CBER had already done this, we proposed to add a regulation (proposed § 601.3) on the issuance of complete response letters concerning BLAs and BLA supplements.

As we stated in the proposed rule, our intent in replacing approvable and not approvable letters with complete response letters is to adopt a more consistent and neutral mechanism to convey that we cannot approve an application in its present form. We believe that issuance of complete response letters will

provide a more consistent approach to informing sponsors of changes that must be made before an application can be approved, with no implication as to the ultimate approvability of the application.

The proposed rule stated our intent to incorporate into the regulations for NDAs the terminology based on the user fee performance goals regarding class 1 and class 2 resubmissions to original NDAs and efficacy supplements. In addition, we proposed to revise our regulations on amendments to unapproved applications, efficacy supplements, and resubmissions to be consistent with user fee performance goals for these amendments.

#### B. Changes to the Proposed Rule

We received 11 comments on the proposed rule. Several comments expressed support for the adoption of complete response letters and for several of the proposed changes to incorporate user fee goals into the regulations. However, some comments objected to certain portions of the proposed rule, including the following:

- The codification of different initial review cycles for human drug applications and supplements to such applications (proposed § 314.100);
- The absence of a provision to allow applicants to request an extension of time in which to submit a resubmission following receipt of a complete response letter (proposed § 314.110(c));

- The review cycle applicable to a resubmission of a supplement other than an efficacy supplement (proposed § 314.110(b)(1)(iii));

- FDA's discretion to defer review of an amendment until the next review cycle (proposed § 314.60(b)).

We address all of the comments in section III of this document.

After considering the comments, we have concluded that it is appropriate to make several revisions to the proposed rule. The final rule deletes the reference in proposed § 314.100(a)(2) to the adjustment of the initial review cycle for human drug applications and supplements to such applications. Adjustment of the initial review cycle to fewer or greater than 180 days for human drug applications and supplements, accepted by mutual agreement between industry and FDA under the agency's user fee performance goals, is provided for under the adjustment by mutual agreement provision in revised § 314.100(c) (see the response to comment 7 in section III.C.1 of this document).

The final rule also revises § 314.110(c) to allow applicants an extension of time in which to resubmit an application, to avoid having the applicant's failure to resubmit within 1 year be regarded as a request to withdraw the application. This revision addresses some comments' concerns that 1 year might not be enough time in which to resubmit an application after receipt of a

complete response letter. The final rule also revises § 314.110(b)(1)(iii) to state that resubmission of an NDA supplement other than an efficacy supplement constitutes an agreement by the applicant to start a new review cycle, beginning on the date we receive the resubmission, that is the same length as the initial review cycle for the supplement (excluding any extension due to a major amendment of the initial supplement).

In addition to these revisions, the final rule includes other changes to the proposed rule in response to comments.

Several comments objected to the regulations in proposed § 314.60(b) that give FDA the option to defer review of different types of amendments until the subsequent review cycle. However, we have determined that we need to have the ability to defer review of amendments to the next review cycle under appropriate circumstances. Although our policy, as reflected in guidance, is to try to review most amendments during the initial review cycle, there are circumstances under which deferral is necessary and appropriate, as discussed in section III.G.1 of this document.

On our own initiative, we also have revised § 314.60(b) to correct an inadvertent omission of a user fee performance goal regarding major amendments to manufacturing supplements. Revised § 314.60(b)(4) now specifies that submission of a major amendment to a manufacturing supplement submitted within 2 months of the

end of the initial review cycle constitutes an agreement to extend the cycle by 2 months.

Also on our own initiative, we have revised the proposed rule to clarify the definition of "efficacy supplement" in § 314.3(b) (21 CFR 314.3(b)), to state the correct address to which requests for a hearing on the denial of approval of an NDA or ANDA must be submitted in § 314.110(b)(3), and to state the correct addresses to which NDAs and ANDAs must be submitted in § 314.440(a)(1) and (a)(2) (21 CFR 314.440(a)(1) and (a)(2)), respectively.

## II. Summary of the Final Rule

### A. Complete Response Letters

We are revising our regulations to substitute complete response letters for approvable and not approvable letters at the completion of the review cycle for an NDA or ANDA. Under revised § 314.110, we will send a complete response letter if we determine that we will not approve an NDA or ANDA in its present form for one or more reasons. A complete response letter usually will describe all of the specific deficiencies that the agency has identified in an application. Table 1 of this document summarizes the changes to our regulations that we are making related to the adoption of complete response letters:

Table 1.--Summary of Changes Regarding Substitution of Complete Response Letters for Approvable and Not Approvable Letters

Previous Regulations	Revised Regulations (changes to proposed rule in italics)
<p><u>Approvable Letter for NDA</u></p> <ul style="list-style-type: none"> <li>• States that NDA is basically approvable if certain issues are resolved.</li> <li>• Indicates that NDA substantially meets requirements of part 314 and FDA can approve it if applicant submits additional information or agrees to specific conditions (e.g., labeling changes).</li> </ul> <p><u>Approvable Letter for ANDA</u></p> <ul style="list-style-type: none"> <li>• Indicates that ANDA substantially meets requirements of part 314 and is approvable if minor deficiencies are corrected.</li> <li>• Describes deficiencies and states when applicant must respond.</li> </ul> <p><u>Not Approvable Letter for NDA or ANDA</u></p> <ul style="list-style-type: none"> <li>• States that NDA cannot be approved for one of reasons in § 314.125 or ANDA cannot be approved for one of reasons in § 314.127.</li> <li>• Describes deficiencies in NDA or ANDA.</li> </ul>	<p><u>Complete Response Letter</u></p> <ul style="list-style-type: none"> <li>• States that FDA will not approve NDA or ANDA in its present form.</li> <li>• Describes all specific deficiencies <u>that FDA has identified in the application</u> (except when the agency determines that data submitted are inadequate to support approval and issues a complete response letter without first conducting required inspection and/or reviewing labeling). Deficiencies could be minor (e.g., requiring labeling changes) or major (e.g., requiring additional clinical trials).</li> <li>• Reflects complete review of data in NDA or ANDA and <u>any amendments FDA has reviewed</u>.</li> <li>• <u>When possible, recommends actions applicant might take to place application in condition for approval.</u></li> </ul>

For products for which approval of a BLA is required for marketing, we are adopting a new regulation, § 601.3, which states that we will send an applicant a complete response letter if we determine that we will not approve a BLA or BLA supplement in its present form.

#### B. Resubmissions

We are revising our regulations on the extension of the review period due to resubmission of an NDA or ANDA after receipt of a complete response letter. A class 2 resubmission of an NDA following receipt of a complete response letter starts a new 6-month review cycle. A class 1 resubmission of an NDA starts a new 2-month review cycle.

These provisions on class 1 and class 2 resubmissions also apply to efficacy supplements to NDAs. For other types of NDA supplements, resubmission starts a new review cycle the same length as the initial review cycle of the supplement under § 314.100(a), excluding any extension due to a major amendment of the initial supplement.

A "major" resubmission of an ANDA following receipt of a complete response letter starts a new 6-month review cycle. A "minor" resubmission of an ANDA starts a new review cycle of an unspecified length; under current FDA guidance, a minor resubmission usually starts a new review cycle of between 30 to 60 days.

The changes to our regulations on applicants' responses to action letters are summarized in the following Table 2.

Table 2.--Summary of Changes to Regulations Regarding Applicant's Response to Agency Action Letters

Previous Regulations	Revised Regulations (changes to proposed rule in italics)
<p><u>Applicant's Response to Approvable Letter or Not Approvable Letter for NDA (or NDA Supplement)</u></p> <p>Within 10 days of date of letter, NDA applicant must do one of following:</p> <ul style="list-style-type: none"> <li>• Amend application or notify FDA of intent to file amendment.</li> <li>• Withdraw application.</li> <li>• Request opportunity for hearing.</li> <li>• Agree to extend review period to decide which of above actions to take.</li> </ul> <p><u>Response to Approvable Letter for ANDA (or ANDA Supplement)</u></p> <ul style="list-style-type: none"> <li>• Correct deficiencies by specified date or FDA will refuse to approve ANDA or ANDA supplement.</li> <li>• Request opportunity for hearing within 10 days.</li> </ul> <p><u>Response to Not Approvable Letter for ANDA (or ANDA</u></p>	<p><u>NDA or ANDA Applicant's Response to Complete Response Letter</u></p> <p>Review period is extended until applicant takes one of following actions:</p> <ul style="list-style-type: none"> <li>• Resubmit NDA or ANDA, addressing identified deficiencies.</li> </ul> <p>-- Class 1 resubmission of NDA or efficacy supplement starts new 2-month review cycle</p> <p>-- Class 2 resubmission of NDA or efficacy supplement starts new 6-month cycle</p> <p>-- Resubmission of NDA supplement other than efficacy supplement starts new cycle same length as <u>initial review cycle for supplement (excluding any extension due to major amendment)</u></p> <p>-- Major resubmission of ANDA or ANDA supplement starts new 6-month cycle</p> <p>-- Minor resubmission of ANDA or ANDA supplement starts new cycle of variable length</p>

<p><u>supplement)</u></p> <ul style="list-style-type: none"> <li>• Same as for NDAs except that 10-day period does not apply (with exception of request for opportunity for hearing).</li> <li>• FDA may regard failure to respond within 180 days as request to withdraw.</li> </ul>	<ul style="list-style-type: none"> <li>• Withdraw NDA or ANDA.</li> <li>• Request opportunity for hearing.</li> </ul> <p>FDA may consider failure to take action within 1 year to be request to withdraw, <u>unless applicant has requested extension of time in which to resubmit.</u></p>
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### C. Amendments to Unapproved Applications

We are also revising our regulations in § 314.60 on extending the review cycle following the submission of an amendment to an unapproved NDA. Under revised § 314.60(b)(1), submission of a major amendment within 3 months of the end of the initial review cycle constitutes an agreement to extend the review cycle by 3 months. Under § 314.60(b)(2), submission of a major amendment more than 3 months before the end of the initial review cycle will not extend the cycle; nor will the initial review cycle for a nonmajor amendment be extended under § 314.60(b)(3). These provisions apply to amendments to original applications, efficacy supplements, and resubmissions of applications and efficacy supplements. Under § 314.60(b)(4), submission of a major amendment to a manufacturing supplement within 2 months of the end of the initial review cycle constitutes an agreement to extend the review cycle by 2 months.

Under § 314.60(b)(5), submission of an amendment to a supplement other than an efficacy or manufacturing supplement will not extend the review cycle. For all of these amendments, we may, at our discretion, defer review of the amendment until the subsequent review cycle, rather than extend the initial cycle or review the amendment during the initial cycle.

Table 3 of this document summarizes the changes to our regulations on amendments submitted before an action letter.

Table 3.--Summary of Changes to Regulations on Amendments Submitted Before Action Letter

Previous Regulations	Revised Regulations (changes to proposed rule in italics)
<p><u>Amendments to Unapproved NDAs and NDA Supplements</u></p> <ul style="list-style-type: none"> <li>• Submission of major amendment constitutes agreement to extend deadline for FDA decision.</li> <li>• FDA may not extend review period more than 180 days.</li> <li>• Submission of nonmajor amendment will not extend review period.</li> </ul>	<p><u>Amendments to Unapproved NDAs, Efficacy Supplements, and Resubmissions of NDAs and Efficacy Supplements</u></p> <ul style="list-style-type: none"> <li>• Submission of major amendment within 3 months of end of initial review cycle may extend cycle by 3 months; FDA may instead defer review to subsequent cycle.</li> <li>• Initial review cycle may be extended only once for major amendment.</li> </ul>
<p><u>Amendments to Unapproved ANDAs and ANDA Supplements</u></p> <ul style="list-style-type: none"> <li>• Submission of amendment containing significant data or information constitutes agreement to extend review period up to 180 days.</li> </ul>	<ul style="list-style-type: none"> <li>• Submission of major amendment more than 3 months before end of initial review cycle will not extend cycle; FDA may instead defer review.</li> <li>• Submission of nonmajor amendment will not extend</li> </ul>

<ul style="list-style-type: none"> <li>• Same for amendments to unapproved ANDA supplements.</li> </ul>	<p>review cycle; FDA may instead defer review.</p> <p><u>Amendments to Unapproved Manufacturing Supplements</u></p> <ul style="list-style-type: none"> <li>• <u>Submission of major amendment within 2 months of end of initial review cycle may extend cycle by 2 months; FDA may instead defer review.</u></li> </ul> <p><u>Amendments to Unapproved NDA Supplements Other Than Efficacy and Manufacturing Supplements</u></p> <ul style="list-style-type: none"> <li>• Submission of any amendment will not extend initial review cycle; FDA may instead defer review.</li> </ul> <p><u>Amendments to Unapproved ANDAs</u></p> <ul style="list-style-type: none"> <li>• Unchanged.</li> </ul>
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### III. Comments on the Proposed Rule

We received written comments from 6 drug manufacturers; 4 associations representing the drug, biologic, and medical device industries; and an individual (11 comments in all). A summary of the comments received and our responses follow.

#### A. General Comments

(Comment 1) One comment stated that throughout the proposed rule the word "response" is used without identifying whose response. As an example, the comment cites proposed

§ 314.101(f)(1)(ii), under which we would issue a notice of opportunity for hearing if an applicant asked us to provide it an opportunity for a hearing on an application "in response to a complete response letter." To clarify whose response is being referenced in a particular provision, the comment recommended that the provision always identify the respondent (e.g., use "an applicant's response to a complete response letter" in the above example).

(Response) We do not believe that it is necessary to revise § 314.101(f)(1)(ii) as requested because only an applicant (not FDA) can respond to a complete response letter as defined in § 314.3(b). We reviewed the other provisions in the proposed rule to ensure that the language does not suggest that the agency might respond to a complete response letter and that the use of the term "response" is not otherwise confusing. We conclude that it is unnecessary to revise the regulations in parts 314, 600, and 601 (21 CFR parts 314, 600, and 601) to identify who is responding to a complete response letter, as it is always the applicant who is responding.

(Comment 2) One comment encouraged us to consider an approval process whereby once we issue an approval letter, the applicant may begin marketing upon notification of approval and not have to address any additional regulatory hurdles, other than

perhaps waiting for the exclusivity period of a previously approved drug to end.

(Response) The comment is beyond the scope of this rulemaking. With the exception of § 314.430 on public disclosure of information in applications, this rule does not address approval or post-approval regulatory matters.

B. Definitions (Proposed § 314.3(b))

1. Class 1 and Class 2 Resubmissions

Proposed § 314.3(b) would have defined "Class 1 resubmission" as the resubmission of an application, following receipt of a complete response letter, that contains final printed labeling, draft labeling, certain safety updates, stability updates to support provisional or final dating periods, commitments to perform Phase 4 studies (including proposals for such studies), assay validation data, final release testing on the last lots used to support approval, minor reanalyses of previously submitted data, and other comparatively minor information.

(Comment 3) Two comments stated that the proposed definition of class 1 resubmission lists items that qualify a resubmission as class 1 and concludes the list with the conjunction "and," implying that a class 1 resubmission contains all of the listed items. The comments recommended that a class 1 resubmission be

defined as a resubmission that "contains one or more of the following" listed items.

(Response) We agree that this change is appropriate and have revised the definition of class 1 resubmission accordingly. Also, on our own initiative, but in a similar spirit of clarifying what was proposed, we are further revising the definition of class 1 resubmission to state that it includes not only the resubmission of an application but also the resubmission of an efficacy supplement. We are making a corresponding revision to the definition of "Class 2 resubmission" in § 314.3. This makes these definitions consistent with the provisions on class 1 and class 2 resubmissions of applications and efficacy supplements in § 314.110(b)(1)(i) and (b)(1)(ii). In addition, because we now refer to Phase 4 studies as "postmarketing" studies (see 21 CFR 314.81(b)(2)(viii)), we are revising the definition of class 1 resubmission accordingly.

(Comment 4) One comment asked how we intended to ensure consistency across review divisions regarding the classification of resubmissions.

(Response) We believe that the definition of class 1 resubmission provides adequate information on the types of resubmissions that are regarded as class 1 resubmissions and, by omission, the types of resubmissions that are regarded as class 2 resubmissions. For several years, CDER review divisions have

been applying these definitions in reviewing resubmissions of applications that are subject to user fees. Nevertheless, CDER will provide training and information to help ensure that the final rule is applied consistently among the review divisions.

## 2. Complete Response Letter

Proposed § 314.3(b) would have defined "complete response letter" as a written communication to an applicant from FDA usually identifying all of the deficiencies in an application or abbreviated application that must be satisfactorily addressed before it can be approved.

(Comment 5) One comment stated that absent unusual circumstances, a complete response letter should clearly define the specific deficiencies in an application to avoid presentation of new issues at a later date and minimize the potential for cycles of complete response letters. Two comments stated that specifying that a complete response letter "usually" identifies all of the deficiencies in an application is contrary to the plain meaning of "complete response" because any response that does not identify all of the deficiencies in an application is not complete. The comments stated that the use of vague language makes the regulation impossible to interpret and leaves the regulatory process open to inconsistencies across divisions. The comments stated that the user fee goals do not include similarly vague language but instead reflect FDA's commitment to review and

act on certain percentages of applications within specified timeframes. The comments noted that the user fee goals state that the term "review and act on" means the issuance of a complete action letter after the complete review of a filed complete application. The comments acknowledged that, for drug products, we might issue a complete response letter without first conducting inspections or reviewing labeling (under proposed § 314.110(a)(3)), but the comments requested that we revise the definition of complete response letter to specify which aspects of a complete review might be postponed while allowing the agency to issue a complete response letter. One of the comments suggested that the definition specify that we may issue a complete response letter "without first conducting required inspections and/or reviewing proposed product labeling when FDA determines that the data submitted are inadequate to support approval as described in § 314.110(a)(3)."

(Response) We do not agree that the definition of complete response letter should be revised as suggested. The statement that a complete response letter "usually" identifies all of the deficiencies in an application is appropriate because § 314.110(a)(1) states that a complete response letter will describe all of the deficiencies "except as stated in paragraph (a)(3) \* \* \*" In turn, paragraph (a)(3) states that if we determine that the data submitted are inadequate to support

approval, we might issue a complete response letter without first conducting required inspections and/or reviewing proposed product labeling. Those are the only circumstances under which the complete response letter would not describe all of the known deficiencies in an application. We do not believe that it is necessary for the definition of complete response letter to specify which particular aspects of a complete review might be postponed.

However, we believe that it is necessary to revise the definition of complete response letter to make clear that a complete response letter is a communication "usually describing all of the deficiencies that the agency has identified in an application or abbreviated application that must be satisfactorily addressed before it can be approved" (§ 314.3(b)). This addresses the possibility that an applicant's response to a deficiency that we have identified in an application might reveal other deficiencies that we had not identified and which we accordingly had been unable to describe in the complete response letter. Although we seek to identify all deficiencies during the initial review period, we sometimes become aware of deficiencies only during a subsequent review period. It would be inconsistent with section 505(d) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(d)) and FDA regulations to approve an application despite an applicant's failure to address

deficiencies solely because those deficiencies were identified only after issuance of a complete response letter, and we do not intend to allow this result.

(Comment 6) One comment recommended that we add to the definition of complete response letter the following statement: "Where appropriate, a complete response letter will describe the actions necessary to place the application in condition for approval."

(Response) Because this statement appears in revised § 314.110(a)(4), we do not believe that it is necessary to add this statement to the definition of complete response letter in § 314.3.

### 3. Efficacy Supplement

Proposed § 314.3(b) would have defined "efficacy supplement" as a supplement to an approved application proposing to make one or more of the following changes to product labeling:

1. Add or modify an indication for use;
2. Revise the dose or dose regimen;
3. Provide for a new route of administration;
4. Make a comparative efficacy claim naming another drug product;
5. Significantly alter the intended patient population;
6. Change the marketing status from prescription to over-the-counter use;

7. Complete the traditional approval of a product originally approved under subpart H of this part; or

8. Incorporate other information based on at least one adequate and well-controlled clinical study.

On our own initiative, we are making three changes to the proposed definition of efficacy supplement. First, we are revising the definition to state that an efficacy supplement means a supplement to an approved application proposing "to make one or more related changes from among the following changes to product labeling \* \* \*". This change makes the definition consistent with our user fee "bundling" policy, which allows certain related changes (such as a change in indication and a related change in dose regimen) to be made in the same supplement with only one fee (see the FDA guidance for industry entitled "Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees").

The second change that we are making to the definition of efficacy supplement is to replace the term "indication for use" (in the first listed change) with the term "indication or claim." The definition of "human drug application" in section 735(1) of the act (21 U.S.C. 379g(1)) includes the term "indication for a use." As part of our user fee assessment policy, we have interpreted the term "indication for a use" more broadly than the term "indication," as the latter term is commonly used (i.e., to

mean a claim that a drug is effective for a particular use, for purposes of complying with the requirements on the content and format of labeling for prescription drugs in 21 CFR 201.57(c). This change clarifies that an efficacy supplement can be submitted to add or modify an indication or claim.

The third change that we are making to the definition of efficacy supplement concerns efficacy supplements that involve the traditional approval of a product that was originally approved under part 314, subpart H, regarding accelerated approval for drugs for serious or life-threatening illnesses. It is possible that an efficacy supplement might be intended to provide evidence of effectiveness for the traditional approval of a subpart H drug but not actually complete the traditional approval of the drug. Therefore, we are revising the definition of efficacy supplement to clarify that such a supplement can be submitted to provide for the traditional approval of a product originally approved under subpart H or to provide evidence of effectiveness necessary for traditional approval of such a product.

C. Timeframes for Review (Proposed § 314.100)

1. Initial Review Cycle

Proposed § 314.100(a)(1) stated that, except as provided in § 314.100(a)(2), within 180 days of receipt of an NDA or ANDA, we will review the application and send the applicant an approval

letter or a complete response letter; this 180-day period is called the initial review cycle. Proposed § 314.100(a)(2) stated that, for drug applications that are human drug applications, as defined in section 735(1)(A) and (B) of the act, or supplements to such applications, as defined in section 735(2) of the act, the initial review cycle will be adjusted to be consistent with the agency's user fee performance goals for reviewing such applications and supplements.

(Comment 7) One comment objected to proposed § 314.100(a)(2), stating that although the user fee goals recognize that we typically do not meet the 180-day statutory review deadline, this should not be memorialized in a regulation. The comment stated that even though the statutory review period is regarded mainly as aspirational, it is important to maintain it within the regulations.

(Response) We agree with the comment that a specific provision solely addressing the adjustment of the initial review cycle for human drug applications and supplements to these applications is not necessary. Therefore, we have deleted proposed § 314.100(a)(2). However, we note that, since the enactment of the Prescription Drug User Fee Act of 1992 (PDUFA) (Public Law 102-571), there has been a mutual understanding between industry and the agency that the review cycle for an application or supplement subject to user fees may be adjusted

(either shortened or lengthened) in accordance with the user fee performance goals. Previous § 314.100(c) provided for an extension of the review cycle by mutual agreement between FDA and an applicant (as well as an extension as a result of a major amendment under §§ 314.60 or 314.96). Consistent with the long-standing approach to applications subject to user fees, we have revised § 314.100(c) to state that the initial review cycle may be adjusted by mutual agreement between FDA and an applicant or as provided in §§ 314.60 and 314.96.

Correspondingly, the final rule also deletes proposed § 314.101(f)(2). Current § 314.101(f)(1) states that within 180 days after the date of filing, plus the period of time the review period was extended (if any), FDA will either approve the application or issue a notice of opportunity for hearing. Proposed § 314.101(f)(2) stated that, for human drug applications and supplements, the 180-day period after the date of filing would be adjusted to be consistent with the user fee performance goals. Proposed § 314.101(f)(2) is not needed because § 314.101(f)(1) encompasses extension of the review period beyond 180 days as well as circumstances under which FDA might approve an application in less than 180 days, regardless of whether such actions are the result of conformance to user fee performance goals.

## 2. Withdrawal and Later Submission

Proposed § 314.100(b) stated that at any time before approval, an applicant may withdraw an application under § 314.65 (21 CFR 314.65) or an abbreviated application under § 314.99 (21 CFR 314.99) and later submit it again for consideration.

(Comment 8) Two comments stated that § 314.100(b) should be revised to address the withdrawal of an application after receipt of a complete response letter. The comments stated that if a complete response letter is followed by withdrawal of the application, the subsequent submission of "the same" application would also constitute a "resubmission." The comments suggested adding the following to § 314.100(b): "Except when preceded by a complete response letter, applications withdrawn prior to approval that are submitted again for the same product are not considered resubmissions as defined in § 314.3(b) of this part."

(Response) We do not agree with the comments because we regard an application that is withdrawn at any time before approval and submitted again for the same product as an original application, rather than a resubmission. The final rule defines "original application" (in § 314.3(b)) as a pending application for which FDA has never issued a complete response letter or approval letter, or an application that was submitted again after FDA had refused to file it or after it was withdrawn without being approved. Under the proposed rule, a "resubmission" was

defined (in proposed § 314.110(b)(1)) as “submission by the applicant of all materials needed to fully address all deficiencies identified in the complete response letter.” Consistent with our approach to applications that are withdrawn before approval and later submitted again, we have added the following statement to the definition of resubmission: “An application or abbreviated application for which FDA issued a complete response letter, but which was withdrawn before approval and later submitted again, is not a resubmission.” For clarity, we are moving the definition of resubmission to § 314.3 from § 314.110(b)(1).

D. Complete Response Letters (Proposed § 314.110)

1. Content of Complete Response Letters

Proposed § 314.110(a) would have required us to send an applicant a complete response letter if we determined that we will not approve the application or abbreviated application in its present form for one or more of the reasons given in § 314.125 or § 314.127, respectively.

(Comment 9) One comment stated that it concurred with our view that the complete response letter should be a neutral mechanism to convey that an application cannot be approved in its present form. The comment agreed that use of the complete response letter will ensure consistency in how sponsors are informed of changes needed for approval, without implying

anything about ultimate approvability. One comment stated that use of the complete response letter will provide a more efficient mechanism for application review.

(Response) As stated in the preamble to the proposed rule, we agree that the use of complete response letters will provide a more neutral and consistent mechanism than the use of approvable and not approvable letters to convey that an application cannot be approved in its present form.

a. Specific deficiencies. Under proposed § 314.110(a)(1), a complete response letter would have described all of the specific deficiencies in an application or abbreviated application, except as stated in § 314.110(a)(3).

(Comment 10) One comment stated that we should clearly identify and define the specific deficiencies in an application when drafting a complete response letter, adding that one purpose of the complete response letter is to minimize paperwork and delays between an applicant and the agency.

(Response) We agree with the comment. The intent of § 314.110(a)(1) is that we will identify and describe all of the known deficiencies (except as provided in § 314.110(a)(3)) to enable applicants to provide appropriate responses. However, consistent with our response to comment 5, we have revised § 314.110(a)(1) to state that a complete response letter will describe all of the specific deficiencies that we have identified

in an application at the time we issue the complete response letter. This change reflects the possibility that we might become aware of certain deficiencies only during a subsequent review period, such as while reviewing an applicant's response to a previously identified deficiency.

(Comment 11) One comment asked that we clarify what mechanisms of communication we will use during the review cycle to convey to sponsors potential deficiencies that we have discovered to enable sponsors to address these deficiencies as quickly as possible. The comment stated that there would be few, if any, applications that would completely satisfy FDA reviewers in the first review cycle.

(Response) Because this comment concerns communication before issuance of the complete response letter, it is beyond the scope of this rulemaking. Nevertheless, it is worth noting that the user fee goals include mechanisms to improve communications about potential deficiencies during the review cycle. For example, the Goals Letter (2002) states that it is the intention of CDER and CBER to notify a sponsor of deficiencies in an application when each discipline has finished its initial review of its section of the pending application. In addition, the Goals Letter states that the review division and the safety group assigned to the review of a particular application will try to communicate their comments on a proposed risk management tool and

plan, as well as on protocols for observational studies, as early in the review process as possible.

b. Complete review of data. Proposed § 314.110(a)(2) stated that a complete response letter reflects our complete review of the data submitted in an original application or abbreviated application (or, where appropriate, a resubmission) and any amendments for which the review cycle was extended. It further stated that the complete response letter will identify any amendments for which the review cycle was not extended that we have not yet reviewed.

(Comment 12) Two comments stated that it was unclear whether complete review of the data includes review of information submitted in major amendments submitted more than 3 months before the end of the initial cycle or nonmajor amendments (which do not trigger extensions under the user fee goals or the proposed rule). The comments stated that the regulation should not define the scope of material included in a complete response letter as "amendments for which the review cycle was extended."

(Response) We agree that § 314.110(a)(2) should include any amendments that we have reviewed, whether or not they resulted in an extension of the review cycle. Therefore, we are revising § 314.110(a)(2) to state that a complete response letter reflects our complete review of the data submitted in an original application or abbreviated application (or, where appropriate, a

resubmission) and any amendments that we have reviewed.

Correspondingly, we are also revising § 314.110(a)(2) to state that the complete response letter will identify any amendments that we have not yet reviewed.

c. Determination that data are inadequate. Under proposed § 314.110(a)(3), if we determined, after an application is filed or an abbreviated application is received, that the data submitted are inadequate to support approval, we might issue a complete response letter without first conducting required inspections and/or reviewing proposed product labeling.

(Comment 13) One comment maintained that stating that we "might" issue a complete response letter without conducting required inspections and/or reviewing labeling adds ambiguity to agency actions. The comment stated that if we determine that the data are inadequate during the first half of the review cycle, it might be acceptable for us to issue a complete response letter without conducting inspections or reviewing labeling; however, a complete response letter sent toward the end of the cycle should thoroughly evaluate all components of the NDA. The comment stated that leaving to the review divisions the decision on whether we issue a complete response letter before we conduct inspections and review the labeling would unintentionally encourage inconsistency. The comment recommended that we revise § 314.110(a)(3) to state that if we determine "early in the

review cycle" or "within the first half of the review cycle" that the data are inadequate, we might issue a complete response letter without conducting inspections or a labeling review.

(Response) We understand the comment's concern about possible uncertainty as to the timing of a decision to issue a complete response letter without conducting an inspection or labeling review. However, it is possible that we might not determine until later in the review cycle that the data in the application are inadequate. Therefore, we believe that it is not appropriate to specify in § 314.110(a)(3) a time after which we could no longer conclude that the data submitted are inadequate to support approval.

(Comment 14) One comment stated no objection to this proposal under the circumstances described but maintained that the complete response letter should indicate the status of each review team (labeling, chemistry and manufacturing, microbiology, bioequivalence, and/or clinical reviews and inspection status).

(Response) Rather than having the complete response letter state the status of each review team, we believe that it is appropriate for the letter to specify what portions, if any, of the review are incomplete, as review of a portion of an application may require input from more than one review team, and it is the status of the portion of a review, not the status of the review team, that is most relevant. This is the approach

that we currently use in issuing approvable and not approvable letters.

(Comment 15) One comment asked us to comment on the future of CDER's Pre-Approval Inspection Program and how it would be incorporated into the proposed new review scheme.

(Response) Inspection of the facilities used in the manufacture of a proposed drug product is an essential part of the application review process. The Pre-Approval Inspection Program will not be affected by this rulemaking.

d. Actions to place application in condition for approval. Proposed § 314.110(a)(4) stated, "Where appropriate," a complete response letter will describe the actions necessary to place the application or abbreviated application in condition for approval.

(Comment 16) One comment stated that we should delete "Where appropriate" from § 314.110(a)(4). The comment stated that a complete response letter should describe the actions and/or specify the data needed to place the application in condition for approval. One comment stated that we should specify precisely the amendments or procedures we will require as an appropriate reply to a complete response letter so that an applicant does not have to guess what is necessary to remedy the deficiencies cited in the letter. The comment stated that this would help applicants address FDA concerns more effectively.

(Response) We agree with the comments that the complete response letter should provide an applicant with information, whenever possible, on what the applicant could do to obtain approval. However, there may be times when what the applicant has submitted to the agency simply does not permit us to specify what the applicant would need to do to put the application in a position for approval. The intent of § 314.110(a)(4) is for us to provide the applicant with sufficient detail on what actions might be necessary to resolve the deficiencies cited in the complete response letter. Providing clear guidance to applicants in the complete response letter will be helpful both to applicants and the agency.

However, at the time of issuance of the complete response letter, we may not have enough information to be certain about precisely what actions, including possibly conducting studies and/or submitting data, may ultimately be necessary to place an application in condition for approval. For example, we might have determined that there is a problem with the formulation of a proposed drug product but not be able to tell the applicant what it could do to resolve the problem, except in a general sense. Because of such potential circumstances, we have replaced "Where appropriate" with "When possible" in § 314.110(a)(4).

In addition, we recognize that although it is appropriate for us to recommend actions that an applicant might take to place

its application in condition for approval, we cannot require an applicant to take specific actions--and only those actions--to obtain approval. There might be multiple acceptable approaches that an applicant could take to remedy a deficiency in its application, and we might lack information that would affect our views on what actions an applicant should take. Therefore, we have revised § 314.110(a)(4) to state that, when possible, a complete response letter will, rather than describe the actions necessary to place an application or abbreviated application in condition for approval, "recommend actions that the applicant might take to place the application or abbreviated application in condition for approval."

## 2. Responses to Complete Response Letters

Under proposed § 314.110(b)(1) to (b)(3), an applicant was required to take one of three actions after receiving a complete response letter: Resubmit the application, withdraw the application, or request an opportunity for a hearing on whether there are grounds for denying approval of the application.

a. Resubmission. Under proposed § 314.110(b)(1), an applicant could, in response to a complete response letter, resubmit the application or abbreviated application, addressing all deficiencies identified in the complete response letter. Proposed § 314.110(b)(1) further stated that, for purposes of § 314.110, a resubmission would mean submission by the applicant

of all materials needed to fully address all deficiencies identified in the complete response letter.

As stated in our response to comment 8, we are relocating the definition of resubmission to § 314.3 from § 314.110(b)(1) and adding a sentence clarifying that an application or abbreviated application for which we issued a complete response letter, but which was withdrawn before approval and later submitted again, is not a resubmission.

i. Resubmission of an NDA supplement other than an efficacy supplement. Under proposed § 314.110(b)(1)(iii), a resubmission of an NDA supplement other than an efficacy supplement would constitute an agreement by the applicant to start a new 6-month review cycle beginning on the date we receive the resubmission.

(Comment 17) Three comments objected to the proposed 6-month cycle for resubmissions of other-than-efficacy supplements. One comment stated that it seemed unreasonable that a resubmission not requiring clinical data would require an additional 6 months for review. Two comments stated that because one of our user fee goals is to act on 90 percent of manufacturing supplements that require prior approval within 4 months, a 6-month review time for a resubmission of such a supplement would be longer than the review time for the original supplement. The comments stated that this is inappropriate because many of these resubmissions need only include data necessary to answer questions from the

initial cycle and do not require as much review time as the initial supplement. The comments recommended that we revise § 314.110(b)(1)(iii) to state that the length of the review cycle for the resubmission of an other-than-efficacy supplement will not exceed that for the original supplement. The comments further recommended that we establish a "Type 1/Type 2" scheme for resubmissions of prior approval chemistry and manufacturing supplements that would be similar to the approach for resubmissions of original applications and efficacy supplements, but with a 2-month review cycle for Type 1 resubmissions and a 4-month cycle for Type 2 resubmissions.

(Response) We agree with the comments that the review cycle for the resubmission of a supplement that is not an efficacy supplement should be the same as the initial review cycle for the original supplement. Therefore, we have revised § 314.110(b)(1)(iii) to state that a resubmission of an NDA supplement other than an efficacy supplement constitutes an agreement by the applicant to start a new review cycle the same length as the initial review cycle for the supplement (excluding any extension due to a major amendment), beginning on the date FDA receives the resubmission. Under § 314.100(a), the initial review cycle for a supplement other than an efficacy supplement is 180 days, unless it is adjusted by mutual agreement or as a result of a major amendment under § 314.100(c). Under revised

§ 314.110(b)(1)(iii), because the initial review cycle for a manufacturing supplement requiring prior approval is 4 months under the user fee goals, the review cycle for a resubmission of a manufacturing supplement would be 4 months (it would not be increased to reflect any extension of the initial review cycle for the manufacturing supplement resulting from a major amendment of the initial supplement). Given this change to § 314.110(b)(1)(iii), we believe that establishing a separate "Type 1/Type 2" classification scheme for resubmissions of prior approval chemistry and manufacturing supplements is not needed to ensure appropriate review cycles for these resubmissions and would create unnecessary administrative burdens.

ii. Minor resubmission of an ANDA. Proposed § 314.110(b)(1)(v) stated that a minor resubmission of an ANDA constitutes an agreement by the applicant to start a new review cycle beginning on the date we receive the resubmission.

(Comment 18) One comment opposed this provision, stating that the failure to specify the length of the new review cycle would seriously hinder an applicant's ability to predict the approval date for its application, resulting in substantial commercial disadvantage. The comment stated that any delay in the onset of launch preparation due to an unpredictable approval date could harm the manufacturer's ability to prepare for the initial marketing of their products. The comment maintained that

without a target date for completion of review, an applicant would be forced to follow up with FDA continually, contrary to requests by CDER's Office of Generic Drugs that applicants follow up only at the targeted time. The comment claimed that the statement in the preamble that the review cycle for a minor resubmission of an ANDA might last "from 30 days to a few months" was contrary to the guidance on "Major, Minor and Telephone Amendments to Abbreviated New Drug Applications" (ANDA amendments guidance), which purportedly was revised to produce more minor amendments and fewer major amendments to move applications through the review process more quickly. The comment maintained that without a definition of "a few months," performance standards would be reduced as much as 50 percent or more, and the distinction between major and minor amendments would blur.

The comment also disagreed with the statement in the preamble that the proposed revisions for ANDA resubmissions are "similar" to those for NDA resubmissions. The comment stated that user fee goals apparently are being implemented at the expense of generic drug manufacturers by reducing the transparency of the review process and extending review times for minor resubmissions. The comment asked that we revise § 314.110(b)(1)(v) to state that minor resubmissions of ANDAs are reviewed 30 to 60 days from receipt. The comment also stated that we should assess the issuance and classification of all

complete response letters to uphold the intent to reduce ANDA approval times and resolve more deficiencies by telephone rather than complete a response letter.

(Response) We do not agree that the provision on minor resubmissions of ANDAs will interfere with generic drug manufacturers' ability to market their products in a timely manner. Under the ANDA amendments guidance, which the Office of Generic Drugs applies to major and minor resubmissions of ANDAs, we attempt to review minor resubmissions within 30 to 60 days, although not all can be reviewed within 60 days. In accordance with the ANDA amendments guidance, we will continue to work closely with ANDA sponsors to provide them with sufficient information about our review of ANDA resubmissions to enable sponsors to plan for the marketing of approved products. We agree with the comment that resolving deficiencies by telephone rather than by complete response letter benefits both applicants and the agency, and we will seek to do so where appropriate in accordance with the ANDA amendments guidance.

b. Request for a hearing. Under proposed § 314.110(b)(3), after receiving a complete response letter, an applicant could ask us to provide it with an opportunity for a hearing on the question of whether there are grounds for denying approval of the NDA or ANDA.

On our own initiative, we have revised § 314.110(b)(3) to update the information on the address to which requests for a hearing on the denial of approval of an NDA or ANDA must be submitted, as a result of the recent relocation of certain CDER offices.

(Comment 19) One comment stated that we should consider having an independent evaluator within FDA attend the hearings to confirm or negate grounds for denying approval. The comment also asked whether these hearings would be open public hearings.

(Response) With respect to the nature of hearings on the denial of approval of applications, § 314.201 states that parts 10 through 16 (21 CFR parts 10 through 16) apply to these hearings. These hearings are not open public hearings; appearance and participation are governed by § 12.40 through § 12.45.

We do not believe that an independent evaluator is needed for hearings on grounds for denial of approval. Section 314.200(f) provides for separation of functions between CDER and the Commissioner of Food and Drugs (the Commissioner) upon receipt of a request for a hearing. CDER prepares an analysis of the request and a proposed order ruling on the issue and submits them to the Commissioner for review and decision. When CDER recommends denial of a hearing on all issues, no CDER representative will participate or advise in the review and

decision by the Commissioner. When CDER recommends that a hearing be granted on one or more issues, separation of functions terminates as to those issues. The Commissioner may modify the text of those issues but may not deny a hearing on those issues. Separation of functions continues with respect to issues on which CDER has recommended denial of a hearing. The Commissioner will neither evaluate nor rule on CDER's recommendation on such issues, and such issues will not be included in the notice of hearing. Participants in the hearing may make a motion to the presiding officer for the inclusion of any such issue in the hearing. Under § 12.60, the presiding officer of any hearing will be the Commissioner, a member of the Commissioner's office to whom responsibility for the matter has been delegated, or an administrative law judge qualified under 5 U.S.C. 3105. Separation of functions on all issues resumes upon issuance of a notice of a hearing. We believe that these provisions provide an adequate means of ensuring that the Commissioner makes an independent assessment of the evidence for and against approval of an application. Therefore, no independent evaluator is needed.

### 3. Failure to Take Action

Under proposed § 314.110(c), an applicant would be considered to agree to extend the review period under section 505(c)(1) of the act until it takes any of the actions listed in

§ 314.110(b) (i.e., resubmission of the application, withdrawal, or request for a hearing). Proposed § 314.110(c) further stated that for an NDA, we might consider an applicant's failure to take any of these actions within 1 year after receiving a complete response letter to be a request by the applicant to withdraw the NDA (for an ANDA, the specified period was 6 months).

(Comment 20) Several comments objected to the elimination of the opportunity, available in previous §§ 314.110(a)(5) and 314.120(a)(5), for an applicant to notify us within 10 days of receipt of an action letter that it agrees to an extension of the review period so that it can determine how to respond further. One comment stated that it was not clear whether any sponsor communication with us regarding an intent to resubmit or amend an application would cancel or postpone the proposed 1-year timeframe. The comment stated that if an applicant believed that it must resubmit within 1 year to avoid automatic withdrawal, the result could be a less-than-complete resubmission. Three comments stated that the absence of a resubmission within 1 year of receipt of a complete response letter cannot reasonably be characterized as failure to take action. Several comments stated that it might take several months for an applicant to reach agreement with us on what studies are needed for approval and then more time to conduct the studies and submit the results.

The comments suggested several ways to revise the regulations to allow applicants to request an extension of the review period. One comment stated that we should expand the first option in § 314.110(b) (resubmission) to permit a sponsor to resubmit its application addressing all deficiencies or state its intent to do so (if the sponsor estimates that it will take more than 1 year to address all deficiencies).

Several comments recommended revisions to § 314.110(c). One comment stated that § 314.110(c) should be revised to clarify that additional time for resubmission will be granted if the applicant is diligently working to address all deficiencies. The comment stated that inaction for 1 year should be regarded as a request to withdraw the application if the applicant has not communicated an intent to resubmit or submitted evidence of progress being made toward the completion of work needed to address all deficiencies.

One comment stated that § 314.110(c) should be revised to allow an applicant to notify us, within a specified time, of its intent to resubmit or to agree to a specified extension of time to reflect an agreed-upon action plan to address deficiencies; absent such notification, we could consider the application withdrawn if it was not resubmitted within 1 year. The comment further stated that if an additional study was required, we should allow an extension beyond the 1-year period.

Two comments recommended that § 314.110(c) be revised in one of two ways. One approach would be to add an option for the applicant to notify us, within a specified time after receipt of a complete response letter, of an intent to resubmit. If the application is not resubmitted within 1 year, the applicant would be required to provide annual confirmation of its intent to resubmit; if the applicant provided no such notification, we could consider the application withdrawn. The alternative approach would require us to notify the applicant requesting a reply within a specified time regarding its intention to resubmit; failure to respond within the specified time would constitute a request for withdrawal.

One comment recommended that applicants be given the option to state their intention to address deficiencies as well as how and when this will be done. The comment suggested that we would use the target date as the closing date for the application. If the applicant later determined that it could not meet this deadline, it could seek another extension, which we could grant or deny at our discretion.

(Response) We agree that proposed § 314.110(c) should be revised to allow applicants to request an extension of time in which to submit a resubmission. We acknowledge that in some circumstances it might take more than 1 year after issuance of a complete response letter for an applicant to reach agreement with

us on what clinical studies might be needed, to conduct any required studies, and to provide the results in a resubmission. Therefore, we are revising § 314.110(c) (renumbered as § 314.110(c)(1)) to state that, for an NDA or ANDA, we may consider an applicant's failure to take any of the actions in § 314.110(b) within 1 year after issuance of a complete response letter to be a request by the applicant to withdraw the application, unless the applicant has requested an extension of time in which to resubmit the application. Section 314.110(c) further states that we will grant any reasonable request for such an extension. In addition, § 314.110(c) states that we may consider an applicant's failure to resubmit the application within the extended time period or to request an additional extension to be a request by the applicant to withdraw the application.

Although, as stated in the proposed rule, ANDA resubmissions usually do not involve generation of clinical data, for consistency we have decided to apply the 1-year period (subject to extension) to ANDA resubmissions as well as NDA resubmissions. In addition, we have revised § 314.110(c)(1) to state that the applicant's 1-year deadline for taking action begins "after issuance of a complete response letter" rather than "after [the applicant] receiv[es]" the complete response letter. This change provides certainty as to the start of the 1-year period. In

addition, on our own initiative we have revised the first sentence of § 314.110(c)(1) to make clear that this paragraph addresses extension of the review period (until any of the actions listed in § 314.110(b) are taken) for an NDA under section 505(c)(1) of the act or an ANDA under section (j)(5)(A) of the act (the proposed rule inadvertently referred only to section 505(c)(1) for NDA applicants).

(Comment 21) Two comments stated that because deeming an application withdrawn is optional under proposed § 314.110(c), differences between and within centers might create an uneven playing field in which some applications are withdrawn while similarly situated applications are not. The comments stated that the decision to withdraw should rest with the applicant.

(Response) We believe that it is reasonable and within the scope of our authority to consider an applicant's failure to take any significant action within a reasonable period of time to be a request to withdraw the application. Nevertheless, we do not believe that § 314.110(c) should require us to deem an application to be withdrawn under these circumstances. Although we agree with the comments that there should not be significant differences across CDER regarding this matter, decisions on whether to regard an applicant's failure to take action as a request to withdraw the application will reflect the circumstances surrounding each particular application.

(Comment 22) One comment stated that we should notify an applicant before deeming an application withdrawn within 1 year for failure to take action under § 314.110(c), and applicants should have reasonable time to respond.

(Response) We agree that it is appropriate for us to notify an applicant that we intend to regard an application as withdrawn for failure to take action. Therefore, we are adding § 314.110(c)(2), which states that if we consider an applicant's failure to take action in accordance with § 314.110(c)(1) to be a request to withdraw the application, we will notify the applicant in writing. Section 314.110(c)(2) further states that the applicant will have 30 days from the date of the notification to explain why the application should not be withdrawn and request an extension of time in which to resubmit the application. Additionally, § 314.110(c)(2) states that we will grant any reasonable request for an extension. Finally, § 314.110(c)(2) states that if the applicant does not respond to the notification within 30 days, the application will be deemed to be withdrawn.

E. Complete Response Letters for BLAs

To incorporate the use of complete response letters into the biologics regulations, the proposed rule added a definition of complete response letter to § 600.3 and added § 601.3 regarding complete response letters. We received comments on these

proposed regulations as well as on the lack of regulations on other matters related to BLAs.

#### 1. General

(Comment 23) One comment stated that although we proposed many changes to § 314.110 regarding complete response letters for NDAs and ANDAs, we proposed only select changes for the corresponding regulations for BLAs in § 601.3. The comment specifically noted the lack of a definition of resubmission in § 601.3 and the fact that NDA and ANDA applicants have three options for responding to a complete response letter under § 314.110(b) while BLA applicants have only two options under § 601.3(b). The comment recommended that we revise § 601.3 to include the topics in § 314.110 or explain the brevity of the biologics regulations. One comment recommended that we revise the biologics regulations to be consistent with the procedures and timeframes for review of resubmissions and amendments of drug applications in part 314.

(Response) BLAs have long been reviewed under procedures and timelines that differ from those for NDAs and ANDAs. In addition, the biologics regulations are less prescriptive and detailed than the NDA and ANDA regulations, and we have relied on guidance documents to specify many of the procedures under which we review BLAs. With respect to the biologics regulations, the proposed rule primarily was intended to codify CBER's practice of

issuing complete response letters for BLAs. A comprehensive revision of the regulations on the review of BLAs was not intended, and we do not believe it is necessary. It also should be noted that although many of the procedures and timeframes in the NDA regulations reflect user fee goals and resources, many of the biological products subject to the licensing regulations in part 601 are not subject to user fees. For these reasons, we will not, at this time, establish more detailed regulations on amendments to BLAs or resubmissions of BLAs following issuance of a complete response letter.

With respect to the two examples of inconsistency noted by one comment, we are adding a definition of resubmission to the biologics regulations at § 600.3 (see the response to comment 27), and we have concluded that it is not necessary that § 601.3(b) specify the right to request a hearing because that right is stated elsewhere in the biologics regulations (see the response to comment 26).

## 2. Definitions (Proposed § 600.3)

Proposed § 600.3(jj) would have defined "complete response letter" as a written communication to an applicant from FDA usually identifying all of the deficiencies in a BLA or BLA supplement that must be satisfactorily addressed before it can be approved.

(Comment 24) Three comments objected to the definition of complete response letter for essentially the same reasons that two of those comments provided for objecting to the definition of complete response letter for NDAs and ANDAs in § 314.3(b). Specifically, the comments maintained that stating that a complete response letter "usually" identifies all of the deficiencies in a BLA that must be satisfactorily addressed is contrary to the plain meaning of "complete response," makes the regulation too vague and open to varying interpretation across review divisions, and is inconsistent with statements in the user fee goals. One comment stated that according to CBER's Standard Operating Procedures and Policies (SOPP) 8405, "Complete Review and Issuance of Action Letters," the complete response letter will summarize all of the deficiencies remaining in a BLA. The comments stated that there might be circumstances when it would be reasonable for us to postpone certain aspects of a complete review; these circumstances, which are set forth in SOPP 8405, are limited to testing of submitted product lots, pre-licensing inspections, and evaluation of final printed labeling.

Two comments recommended that the definition of complete response letter for BLAs specifically note those aspects of a complete review that may be postponed while allowing the agency to issue the letter. One of those comments specifically recommended defining a complete response letter as "a written

communication to the applicant from FDA identifying all of the specific deficiencies in a biologics license application or supplement that must be satisfactorily addressed before it can be approved. A complete response letter may be issued without conducting testing of submitted product lots, required inspections, or evaluation of final printed labeling or suitable alternative." One comment recommended that the definition state that a complete response letter identifies all deficiencies in a BLA "except when such communication is issued without conducting testing of submitted product lots, required inspections, or evaluation of final printed labeling." The comment recommended that the preamble to the final rule state that "evaluation of final printed labeling" does not include the communication of deficiencies pertaining to intended use or product claims. The comment stated that early communication and resolution of such items are critical to efficient review, and deficiencies in these areas might require additional studies.

(Response) We agree with the comments that, generally, a complete response letter will identify all of the deficiencies in a BLA. Consistent with our response to comment 5, we have revised the definition of complete response letter in § 600.3 to state that a complete response letter is a communication "usually describing all of the deficiencies that the agency has identified in a biologics license application or supplement that must be

satisfactorily addressed before it can be approved.” (The definition of complete response letter is set forth in § 600.3(ll), rather than § 600.3(jj) as proposed, because two other definitions have been added to § 600.3 since the issuance of the proposed rule.) We also agree with the comments that exceptions to this general rule include when the complete response letter concerns a BLA with respect to which we have not conducted required inspections, tested product lots, and/or reviewed proposed product labeling. Therefore, we are revising § 601.3(a) (rather than the definition of complete response letter in § 600.3) to state in § 601.3(a)(1) that a complete response letter will describe all of the deficiencies that the agency has identified in a BLA or BLA supplement, except as stated in § 601.3(a)(2). Section 601.3(a)(2) states that if we determine, after a BLA or BLA supplement is filed, that the data are inadequate to support approval, we might issue a complete response letter without first conducting required inspections, testing submitted product lots, and/or reviewing proposed product labeling. The provision refers to proposed product labeling rather than the suggested final printed labeling because we generally review the latter only after an applicant has addressed any major deficiencies in an application.

(Comment 25) One comment stated that the definition of complete response letter should include the statement, “Where

appropriate, a complete response letter will describe the actions necessary to place the application in condition for approval.”

(Response) Consistent with § 314.110(a)(4) (see our response to comment 16), we have added the following statement in § 601.3(a)(3) (rather than to the definition of complete response letter in § 600.3): “When possible, a complete response letter will recommend actions that the applicant might take to place its biologics license application or supplement in condition for approval.”

### 3. Complete Response Letter (Proposed § 601.3)

a. Complete response letter. Proposed § 601.3(a) stated that we would send the BLA applicant or BLA supplement applicant a complete response letter if we determined that we would not approve the application or supplement in its present form. As stated in our response to comment 24, we have added § 601.3(a)(1) stating that a complete response letter will describe all of the deficiencies that the agency has identified in a BLA or BLA supplement, except as stated in § 601.3(a)(2). As discussed in our response to comment 25, we also are adding § 601.3(a)(3) stating that, when possible, a complete response letter will recommend actions that the applicant might take to place its BLA or BLA supplement in condition for approval.

b. Applicant actions. i. General. Under proposed § 601.3(b), after receiving a complete response letter, the

biologics license applicant or supplement applicant was required to either resubmit the application or supplement or withdraw it.

(Comment 26) One comment stated that although NDA and ANDA applicants have three options following receipt of a complete response letter (resubmit the application, withdraw it, or request a hearing), BLA applicants have only two options (resubmit or withdraw the application). The comment recommended that we either revise § 601.3 or explain this omission from the biologics regulations.

(Response) We do not believe that it is necessary to include, in § 601.3, a reference to the option to request a hearing. Under § 601.4(b) (21 CFR 601.4(b)), if we determine that an establishment or product that is the subject of a BLA does not meet the requirements for approval, we will deny the BLA and inform the applicant of the grounds for, and of an opportunity for a hearing on, the decision. Section 601.4(b) further states that if the applicant requests, we will issue a notice of opportunity for a hearing on the matter pursuant to § 12.21(b). Because the right to request a hearing regarding a denial of approval is set forth in § 601.4(b), we do not believe that it is necessary to revise § 601.3 as requested.

ii. Resubmission. Under proposed § 601.3(b)(1), after receiving a complete response letter, a BLA applicant or supplement applicant could resubmit the application or

supplement, addressing all deficiencies identified in the complete response letter.

(Comment 27) Two comments stated that describing a resubmission without any qualifying language appears to require resubmission of the original application or supplement (as opposed to a resubmission limited to responses to the deficiencies listed in the complete response letter). Three comments recommended that the biologics regulations include a definition of resubmission.

(Response) We agree that the regulations should define "resubmission." Therefore, we have added a definition of resubmission in § 600.3(mm), stating that a resubmission is a submission by the biologics license applicant or supplement applicant of all materials needed to fully address all deficiencies identified in the complete response letter. This parallels the definition of resubmission in § 314.3(b).

(Comment 28) Two comments stated that the biologics regulations (like the drug regulations) should clarify that applications withdrawn prior to approval that are submitted again for the same product are not considered resubmissions.

(Response) We agree. Therefore, consistent with the definition of resubmission in § 314.3(b) for NDAs and ANDAs (see the response to comment 8), the definition of resubmission in § 600.3(mm) includes the statement, "A biologics license

application or supplement for which FDA issued a complete response letter, but which was withdrawn before approval and later submitted again, is not a resubmission."

c. Failure to take action. Under proposed § 601.3(c), we could consider a BLA applicant or BLA supplement applicant's failure to either resubmit or withdraw the application or supplement within 1 year after receiving a complete response letter to be a request by the applicant to withdraw the application or supplement.

(Comment 29) As with proposed § 314.110(c) concerning complete response letters to NDA and ANDA applicants, several comments objected to the lack of an option in § 601.3(c) to seek an extension of time in which to resubmit an application or supplement. Two comments stated that the absence of a resubmission within 1 year of receipt of a complete response letter cannot reasonably be characterized as failure to take action. Three comments stated that it might take at least several months for an applicant to reach agreement with us on what studies are needed for approval and then more time to conduct the studies and submit the results. One comment maintained that although the preamble to the proposed rule stated that § 601.3 is intended to incorporate current CBER policy, § 601.3(c) does not reflect current policy and does not afford applicants the opportunity to notify us of their intent to

resubmit an application to prevent us from considering it withdrawn.

Four comments suggested revisions to § 601.3(c). One comment recommended that it be revised to state as follows: "FDA may consider a biologics license applicant or supplement applicant's failure to resubmit, amend the application to request an extension of time to respond, or withdraw the application or supplement within 1 year after receiving a complete response letter to be a request by the applicant to withdraw the application or supplement." One comment recommended that the first option in proposed § 601.3(b) be revised to permit sponsors to resubmit the BLA or supplement addressing all deficiencies or state their intention to do so (if they conclude that it will take more than 1 year to address all deficiencies).

Two comments recommended that § 601.3(c) be revised in one of two ways. One approach would be to add an option for the BLA or BLA supplement applicant to notify us, within a specified time after receipt of a complete response letter, of an intent to resubmit. If the resubmission is not submitted within 1 year, the applicant would be required to provide annual confirmation of its intent to resubmit; if the applicant provides no such notification, we could consider the application or supplement withdrawn. The alternative approach would require us to notify the applicant requesting a reply within a specified time

regarding its intention to resubmit; failure to respond within the specified time would constitute a request for withdrawal.

(Response) For the reasons stated in the discussion of § 314.110(c) (see the response to comments 20 and 22), we agree that § 601.3(c) should be revised to, among other things, allow applicants to seek an extension of time in which to resubmit an application (beyond 1 year after issuance of the complete response letter), and to notify applicants when we decide to consider an applicant's failure to take action as required under § 601.3 to be a request to withdraw the application. Therefore, we are revising § 601.3(c) to state, in § 601.3(c)(1), that we may consider a BLA applicant or BLA supplement applicant's failure to either resubmit or withdraw the application or supplement within 1 year after issuance of a complete response letter to be a request by the applicant to withdraw the application or supplement, unless the applicant has requested an extension of time in which to resubmit the application or supplement. Section 601.3(c)(1) further states that we will grant any reasonable request for such an extension. Finally, § 601.3(c)(1) states that we may consider an applicant's failure to resubmit the application or supplement within the extended time period or to request an additional extension to be a request by the applicant to withdraw the application.

We also are adding § 601.3(c)(2), which states that if we consider an applicant's failure to take action in accordance with § 601.3(c)(1) to be a request to withdraw the application, we will notify the applicant in writing. Section 601.3(c)(2) further states that the applicant will have 30 days from the date of the notification to explain why the application or supplement should not be withdrawn and request an extension of time in which to resubmit the application or supplement, and we will grant any reasonable request for an extension. Finally, § 601.3(c)(2) states that if the applicant does not respond to the notification within 30 days, the application or supplement will be deemed to be withdrawn.

As with revised § 314.110(c)(1), we are substituting the phrase "after issuance of a complete response letter" for the phrase "after receiving a complete response letter" to provide certainty about the start of the 1-year period.

#### F. Miscellaneous Provisions Related to Complete Response Letters

##### 1. Content and Format of Applications (Proposed § 314.50)

Proposed § 314.50(d)(5)(vi)(b) would have required NDA applicants to submit safety update reports 4 months after the initial submission, in a resubmission following receipt of a complete response letter, and at other times as requested by us. Previous § 314.50(d)(5)(vi)(b) had required the submission of safety updates 4 months after the initial submission, after

receiving an approvable letter, and when otherwise requested by us.

(Comment 30) One comment stated that in most cases, a sponsor would receive the complete response letter toward the end of the initial cycle, normally well after it had submitted the traditional 4-month safety update. The comment stated that the amount of data needed in a resubmission could be substantial if there are many ongoing studies. Therefore, the comment requested that we include in the preamble to the final rule general guidance on whether there would be any difference in expectations on the content of the safety update provided in the resubmission.

(Response) We will expect applicants to provide the same type of data and other information in safety updates included in a resubmission as we did with safety updates included in a resubmission following receipt of a not approvable letter. Not approvable letters set forth in detail the information that we expected applicants to include in the safety update. As the comment suggests, this could include substantial information regarding any ongoing clinical studies. We will expect applicants to provide the same level of information in a resubmission following receipt of a complete response letter.

2. Withdrawal by the Applicant of an Unapproved Application  
(Proposed § 314.65)

Proposed § 314.65 stated in part that if, by the time we received notice of an applicant's request to withdraw an unapproved application, we had identified any deficiencies in the application, we would list such deficiencies in the letter we sent the applicant acknowledging the withdrawal.

(Comment 31) One comment stated that all communications before the issuance of approval or tentative approval should remain confidential. Therefore, the comment recommended that the following statement be added to § 314.65: "This communication, like all communications prior to approval or tentative approval, will not be publicly disclosed."

(Response) We agree with the comment that the letter to an applicant acknowledging the withdrawal of its application is a confidential communication. However, we do not believe that it is necessary to add to § 314.65 the language suggested by the comment. The confidential nature of such communications is already addressed in § 314.430.

3. Public Disclosure of Existence of Applications (Proposed § 314.430)

Proposed § 314.430(b) stated that we would not publicly disclose the existence of an application or abbreviated application before an approval letter was sent to the applicant

under § 314.105 or a tentative approval letter was sent to the applicant under § 314.107, unless the existence of the application or abbreviated application had been previously publicly disclosed or acknowledged. Previous § 314.430(b) stated that we would not make such a disclosure before issuance of an approvable letter. In the proposed rule, we acknowledged that our proposed change might result in later disclosure than sometimes occurred under the previous regulation with respect to those applications for which we issued approvable letters. But we stated that the proposed change was consistent with our presumption that, before approval, the existence of an application is confidential commercial information under § 20.61 (21 CFR 20.61). However, we invited comment on whether it would be appropriate for us to disclose the existence of an application following issuance of a complete response letter and, if so, under what conditions.

(Comment 32) Six comments agreed with the proposal to not disclose the existence of an NDA or ANDA before we send an approval letter or tentative approval letter unless the existence of the application has been previously publicly disclosed or acknowledged. Two comments stated that it was appropriate to continue our current policy on disclosure; one comment stated that this was consistent with the presumption that the existence of an application is confidential commercial information. One

comment specifically opposed the alternative approach we suggested in the proposed rule, under which we could disclose the existence of an NDA or ANDA following issuance of a complete response letter unless the applicant notified us by a specified date that the applicant had not publicly disclosed or acknowledged the application's existence. The comment stated that such disclosure could be harmful, particularly in the generic drug sector, to any competitive advantage that a sponsor might have in a race to product launch. The comment also agreed with the statement in the proposed rule that requiring applicants to notify us to prevent our disclosing the existence of their applications would create the potential for error and would be burdensome.

One comment preferred the alternative approach suggested in the proposed rule. One comment, although opposed to routine disclosure of the existence of an application following issuance of a complete response letter, appeared to suggest that we revise the regulation to state that we could make such a disclosure provided the applicant asked us to do so within 10 days of receipt of the complete response letter. The comment stated that this would place the onus on the applicant to request disclosure and would prevent inadvertent disclosure by the agency prior to approval.

(Response) We believe that it is appropriate to not publicly disclose the existence of an NDA or ANDA (unless the existence has already been disclosed or acknowledged) until we have issued an approval letter or tentative approval letter for that application. As we stated in the preamble to the proposed rule, this is consistent with our long-standing presumption that before approval or tentative approval, the existence of an application is confidential commercial information. In addition, we believe that this approach is preferable to one that would require applicants to notify us, after issuance of a complete response letter, that they object to disclosure. As we stated in the preamble to the proposed rule, such a notification system would create the potential for inadvertent disclosure and pose administrative burdens for applicants and the agency. Similarly, we do not believe that it is appropriate to codify a procedure under which an applicant could notify us that we may disclose the existence of its application. An applicant may publicly disclose the existence of its application at any time.

#### 4. Addresses for Applications and Abbreviated Applications

(Proposed § 314.440)

The proposed rule would have revised § 314.440(a)(1) to state that, except as provided in § 314.440(a)(4), an application under § 314.50 or § 314.54 submitted for filing should be

directed to the Central Document Room, 12229 Wilkins Ave.,  
Rockville, MD 20852-1833.

The proposed rule correctly revised the title of the office to which applications must be submitted under § 314.440(a)(1) from "Document and Records Section" to "Central Document Room," but it inadvertently changed the address for the office. The final rule states the correct address to which these applications must be submitted as follows: Central Document Room, 5901-B Ammendale Rd., Beltsville, MD 20705-1266.

In addition, on our own initiative we are revising § 314.440(a)(2) concerning addresses for ANDAs to specify the current address for the Office of Generic Drugs and to update related information.

G. Amendments to NDAs (Proposed § 314.60)

We proposed several revisions to § 314.60 concerning amendments to unapproved NDAs. Previous § 314.60 stated in part that submission of a major amendment ordinarily would extend the application's review period only for the time necessary to review the new information, but not more than 180 days; submission of an amendment that was not a major amendment would not extend the review period. We proposed to revise § 314.60 to, among other things, specify how long the review cycle would be extended for several types of amendments. In addition, proposed § 314.60(b)

would allow us to defer all of these amendments to the next review cycle.

#### 1. General

(Comment 33) Several comments objected to the proposal to give us discretion to defer review of these amendments. One comment stated that unilateral deferrals by FDA are inappropriate and requested that we explain the conditions under which reviews would be deferred. Two comments stated that the user fee goals do not suggest that we should have an unlimited option to unilaterally defer review of amendments. The comments maintained that the user fee goal concerning extension of the review cycle for a major amendment submitted within 3 months of the end of the review cycle was intended to encourage a single, contiguous review leading to a complete response. These comments recognized, however, that deferral might sometimes result in more efficient review and effective use of resources. Therefore, the comments recommended that the regulations list the specific conditions under which we could defer review of amendments.

One comment stated that the regulations should emphasize that we will ordinarily strive to complete full review of an application, including amendments, by the user fee goal date. The comment maintained that deferral of review is only appropriate if an amendment is submitted so late in the cycle that it cannot be reviewed by the goal date or contribute to an

approval decision because there are other major deficiencies that cannot be addressed in the initial cycle.

(Response) We do not agree with the comments concerning our discretion to defer review of amendments. We believe that it is necessary for the efficient review of applications for us to have the ability to defer review of amendments where appropriate. Our current policy on the review of amendments is set forth in our guidance document entitled "Good Review Management Principles and Practices for PDUFA Products" (the GRMP guidance). The GRMP guidance states that during the initial review cycle, we ordinarily review all amendments that we ask the applicant to make during the review and any amendments previously agreed upon (e.g., during the pre-NDA/BLA meeting). The guidance further states that we might review substantial amendments submitted late in the review cycle during a subsequent cycle, depending, in part, on other identified deficiencies. As for all other amendments, the guidance states that we attempt to review them during the first review cycle but might not be able to do so or might decide not to do so in some circumstances (e.g., when the content of such an amendment does not address a known deficiency in the application).

The GRMP guidance notes that under the user fee goals, submission of a major amendment during the last 3 months of a review may trigger a 3-month extension of the review clock. The

guidance states that we decide whether to extend the review clock based on consideration of a variety of factors, including content of the amendment, FDA workload and resources, and the existence of other known deficiencies possibly affecting approval that have not been addressed by the amendment. The guidance states that the underlying principle guiding our decision is to consider the most efficient path toward completion of a comprehensive review that addresses the deficiencies in an application and leads toward a first cycle approval when possible.

As the GRMP guidance states, although we strive to review amendments during the initial review cycle for an application, there are circumstances under which this is not possible or would not be an efficient use of resources. Although the GRMP guidance specifies some of the circumstances in which deferral of review of an amendment to the next review cycle might be appropriate, we do not believe that we can codify in the regulations all of the circumstances under which we might defer review of an amendment. Therefore, we conclude that § 314.60 must provide us with the discretion to defer review of various types of amendments until the subsequent review cycle, when appropriate.

(Comment 34) Two comments stated that § 314.60 should require us to provide written notification to the applicant when we defer an amendment to the next cycle because deferral is essentially an action decision. The comments stated that such

notification should describe the deficiencies that preclude approval.

(Response) We agree with the comments that we should provide written notification to an applicant when we defer review of an amendment to the subsequent review cycle. We currently provide such notice in our approvable and not approvable letters.

Therefore, we have added a new § 314.60(b)(7) stating as follows:

“When FDA defers review of an amendment until the subsequent review cycle, the agency will notify the applicant of the deferral in the complete response letter sent to the applicant under § 314.110.” We do not believe that it is necessary to codify in the regulations that we will provide a reason for the deferral. Usually, the reasons for deferral are general in nature (e.g., the amendment contains substantial new information or does not address a known deficiency). We would be willing to discuss the reasons for deferral after the applicant receives the complete response letter.

## 2. Major Amendment Within 3 Months of the End of the Cycle

(Proposed § 314.60(b)(1))

Under proposed § 314.60(b)(1), submission of a major amendment to an original application, efficacy supplement, or resubmission of an application or efficacy supplement within 3 months of the end of the initial review cycle constituted an agreement by the applicant under section 505(c) of the act to

extend the initial review cycle by 3 months. Proposed § 314.60(b)(1) further stated that we might instead defer review of the amendment until the subsequent review cycle. Proposed § 314.60(b)(1) also stated that the initial review cycle for an original application, efficacy supplement, or resubmission of an application or efficacy supplement may be extended only once due to the submission of a major amendment. It further stated that we might, at our discretion, review any subsequent major amendment during the initial review cycle (as extended) or defer review to the subsequent cycle.

On our own initiative, we are revising § 314.60(b)(1) with respect to amendments to resubmissions. Unlike applications and supplements (21 CFR 314.71(c)), resubmissions are not subject to the "initial review cycle" provision in § 314.100(a); they just have a "review cycle." Therefore, we are adding to § 314.60(b)(1) a statement clarifying that, for references to a resubmission of an application or efficacy supplement in § 314.60(b), the timeframe for reviewing the resubmission is the "review cycle" rather than the "initial review cycle."

(Comment 35) One comment stated that, for clarity, the regulations should include a definition of "major amendment."

(Response) We do not believe that it is necessary to include a definition of major amendment in the regulations. Previous § 314.60(a) did not define a major amendment; it only gave an

example of a major amendment (i.e., "an amendment that contains significant new data from a previously unreported study or detailed new analyses of previously submitted data"). Because we are uncertain that we can define major amendment in a way that encompasses all types of amendments that should be treated as major amendments, we decline to add a definition to the regulations.

(Comment 36) Two comments recommended not codifying the 3-month extension for a major amendment submitted within 3 months of the end of the initial review cycle because, although this is consistent with current user fee goals, those goals could change as a result of future negotiations on user fees. The comments stated that the timeframes agreed upon in the user fee negotiations historically have taken precedence over existing regulatory timeframes, as was recognized in proposed § 314.100(a)(2). The comments stated that if we believed it was necessary to codify user fee goals on extensions, we should revise § 314.60(b) to state that for human drug applications, any extension of review due to a major amendment will be consistent with the user fee goals, similar to proposed § 314.100(a)(2).

(Response) As stated in the preamble to the proposed rule, we are revising § 314.60 to state that submission of a major amendment within 3 months of the end of the review cycle will extend the review cycle by 3 months because we want to make the

regulation consistent with the current user fee goal on these amendments. At present, we do not anticipate a change in this goal. If this goal does in fact change as a result of a future user fee agreement, we could issue a proposed rule proposing to make the regulation match the user fee goal on this matter.

(Comment 37) Four comments specifically addressed the provision in proposed § 314.60(b)(1) allowing deferral of review of a major amendment submitted within 3 months of the end of the initial review cycle. One comment stated that the option to defer review was arbitrary and inconsistent with the user fee goals. The comment stated that neither the proposed codified provision nor the preamble gave examples of when it might be appropriate to defer review. The comment claimed that because the overwhelming majority of these amendments are submitted in response to FDA requests, it would be unreasonable to penalize applicants by deferring review of the amendments. The comment also stated that early communication of information and data requests in accordance with GRMP principles will ordinarily result in receipt of responses early in the initial cycle, giving us more time to complete our review by the goal date. Therefore, the comment recommended that § 314.60(b)(1) be revised to state that the agency will make every effort to complete its review of the full application, including amendments, by the user fee goal date. The comment maintained that review of these major

amendments should only be deferred when the amount of new information and the timing of the submission make it impossible to review the amendment in the initial cycle.

One comment recommended revising § 314.60(b)(1) to state that we would not be required to review a major amendment that pertains to one section of the application if we have previously identified deficiencies in another section that prevent first-cycle approval. Two comments recommended revising § 314.60(b)(1) to state that we may defer review of a major amendment submitted within the last 3 months of the initial cycle that meets any of the following criteria: (1) It amends technical sections of an application in which we have identified deficiencies that prohibit approval during the initial cycle and that do not contain information needed to put the application in condition for approval; (2) it amends a technical section other than sections in which we have identified deficiencies preventing approval, where review of the amendment will not result in approval during the current cycle; or (3) it is an amendment for which, under the user fee goals, we could not extend the review cycle (e.g., a second major amendment submitted within the last 3 months of the initial cycle).

(Response) We do not agree with any of the proposed revisions to § 314.60(b)(1). As stated in the GRMP guidance, we usually seek to review amendments, including major amendments,

during the initial review cycle. However, we do not believe that it is necessary to codify this intent in § 314.60(b)(1) or elsewhere in this section. As stated in our response to comment 33, we do not believe that we can codify all of the circumstances under which it might be appropriate to defer review of major amendments. In addition, we do not agree with the claim that the overwhelming majority of amendments are submitted in response to agency requests, and the comment provides no evidence supporting this statement. For these reasons, we believe that it is appropriate to include in § 314.60(b)(1) a statement that we can defer review of a major amendment submitted within 3 months of the end of the initial review cycle rather than extend the cycle by 3 months.

(Comment 38) One comment stated that § 314.60(b)(1) also should specify that we would not be required to review a second major amendment submitted within 3 months of the goal date with no accompanying extension of the review clock.

(Response) We do not agree with the suggested change. Proposed § 314.60(b)(1) stated that the initial review cycle may be extended only once due to the submission of a major amendment, and any subsequent major amendment would either be reviewed during the initial review cycle or deferred. We believe that it is appropriate that § 314.60(b)(1) include these provisions to

make clear that we will not extend the review cycle for a second major amendment.

### 3. Major Amendment More Than 3 Months Before the End of the Cycle (Proposed § 314.60(b)(2))

Under proposed § 314.60(b)(2), submission of a major amendment to an original application, efficacy supplement, or resubmission of an application or efficacy supplement more than 3 months before the end of the initial review cycle would not have extended the cycle. Proposed § 314.60(b)(2) further stated that we might, at our discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

(Comment 39) One comment stated that the deferral provision in § 314.60(b)(2) would have the unintended effect of widening differences among review divisions regarding when review of these major amendments is deferred and would seem to discourage the possibility of dialogue on the merits of submission of a major amendment. Two comments stated that, because the user fee goals do not address major amendments submitted more than 3 months before the end of the review period, the implication is that review can be accommodated during the initial cycle. One comment stated that we should not defer the review of major amendments submitted well in advance of the goal date, so this option should be deleted from the rule. One comment recommended that

§ 314.60(b)(2) state that we will ordinarily make every effort to complete our review of an application or efficacy supplement, including any amendments submitted more than 3 months before the end of the initial cycle, by the user fee goal date.

Several comments stated that the regulation should specify the criteria under which we could defer review of these major amendments. Two comments recommended that § 314.60(b)(2) state that we may defer review of a major amendment submitted more than 3 months before the end of the initial cycle when we have already identified at least one major deficiency (such as a failed pivotal trial) that is not addressed by the amendment and is unlikely to be addressed during the current cycle due to a need for significant additional research or development.

(Response) We do not agree with any of the proposed revisions to § 314.60(b)(2). For the reasons stated in our response to comment 33, we do not believe that we can codify all of the circumstances under which it might be appropriate to defer review of these major amendments. Consequently, we have retained the provision in § 314.60(b)(2) giving us the discretion to defer review of these amendments to the next review cycle.

#### 4. Nonmajor Amendment (Proposed § 314.60(b)(3))

Under proposed § 314.60(b)(3), the submission of an amendment to an original application, efficacy supplement, or resubmission of an application or efficacy supplement that is not

a major amendment would not have extended the initial review cycle. Proposed § 314.60(b)(3) further stated that we might, at our discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

(Comment 40) One comment stated that § 314.60(b)(3) would have the unintended effect of widening differences in interpretation among review divisions regarding these nonmajor amendments. The comment added that § 314.60(b)(3) seemed contrary to § 314.102(b), which encourages reviewers to communicate promptly to applicants easily correctable deficiencies so that the deficiencies can be corrected through amendments before the review period ends. One comment stated that by their very nature, these amendments are less complex and require less time to review, which provides even more reason to expect that they be reviewed in the initial cycle. Therefore, the comment maintained that § 314.60(b)(3) should state that we will ordinarily review all nonmajor amendments by the user fee goal date.

Several comments stated that § 314.60(b)(3) should set forth the criteria for deferral of review. One comment recommended that § 314.60(b)(3) state that we could defer review of a nonmajor amendment that is submitted close to the end of the cycle and which could not contribute to an approval decision because other major deficiencies cannot be satisfactorily

addressed. One comment suggested that the regulation state that we could defer review if a nonmajor amendment is submitted late in the review cycle (such as 1 to 2 months before the end) or if the amendment does not provide information that addresses easily correctable deficiencies, provided other major deficiencies prevent approval at the end of the initial cycle. Similarly, two comments recommended that § 314.60(b)(3) state that we may defer review of a nonmajor amendment that is received within 1 month of the end of the initial cycle or that does not contain information adequate to put the application in condition for approval during the current cycle. One comment recommended stating that we could defer review of a nonmajor amendment that is received late in the review cycle (e.g., within weeks of the goal date) when review of the amendment is not expected to impact the outcome of the application review.

(Response) We do not agree with any of the proposed revisions to § 314.60(b)(3). For the reasons stated in our response to comment 33, we do not believe that we can codify all of the circumstances under which it might be appropriate to defer review of these nonmajor amendments. Consequently, we have retained the provision in § 314.60(b)(3) giving us the discretion to defer review of these amendments to the next review cycle.

5. Amendment to Supplement Other Than Efficacy Supplement  
(Proposed § 314.60(b)(4))

Under proposed § 314.60(b)(4), submission of an amendment to a supplement other than an efficacy supplement would not have extended the initial review cycle. Proposed § 314.60(b)(4) further stated that we might, at our discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

On our own initiative, we have revised § 314.60(b)(4) to ensure that the regulation is consistent with the user fee performance goal regarding major amendments to manufacturing supplements. In PDUFA III, industry and the agency agreed that submission of a major amendment to a manufacturing supplement submitted within 2 months of the goal date would extend the goal date for acting on the supplement by 2 months, and that there can be only one such extension per review cycle. Although industry and the agency have been acting in accordance with this user fee goal since the enactment of PDUFA III in 2002, we inadvertently failed to incorporate this practice into the proposed rule issued in 2004. Consequently, we have revised § 314.60(b)(4) to state that submission of a major amendment to a manufacturing supplement within 2 months of the end of the initial review cycle constitutes an agreement by the applicant under section 505(c) of the act to extend the initial review cycle by 2 months.

Consistent with the approach to major amendments in § 314.60(b)(2), revised § 314.60(b)(4) further states: FDA may instead defer review of a major amendment to a manufacturing supplement until the subsequent review cycle; if we extend the initial review cycle, the division responsible for reviewing the supplement will notify the applicant of the extension; the initial review cycle for a manufacturing supplement may be extended only once due to submission of a major amendment; and we may, at our discretion, review any subsequent major amendment during the initial review cycle (as extended) or defer review until the subsequent review cycle.

In accordance with the change to § 314.60(b)(4), revised § 314.60(b)(5) states that submission of an amendment to a supplement other than an efficacy or manufacturing supplement will not extend the initial review cycle, and we have discretion to review or defer review of such an amendment. Proposed § 314.60(b)(5) has been renumbered as § 314.60(b)(6).

(Comment 41) One comment recommended that we revise proposed § 314.60(b)(4) to state that we might consider deferring review of other-than-efficacy supplements that are received late in the review cycle (e.g., within weeks of the goal date) when their review is not expected to impact the outcome of the application review. Two comments stated that the regulation should permit us to defer review of any other-than-efficacy supplement that either

is received within 1 month of the end of the initial cycle or contains information that is inadequate to put the application in condition for approval during the current cycle.

(Response) We do not agree with either of the suggested revisions to proposed § 314.60(b)(4) (now § 314.60(b)(5)). For the reasons stated in our response to comment 33, we do not believe that we can codify all of the circumstances under which it might be appropriate to defer review of amendments to supplements other than efficacy or manufacturing supplements. Consequently, we have retained the provision in § 314.60(b)(5) giving us the discretion to defer review of these amendments to the next review cycle.

#### 6. Contents of Major Amendment (Proposed § 314.60(b)(5))

Under proposed § 314.60(b)(5) (now § 314.60(b)(6)), a major amendment could not include data to support an indication for a use that was not included in the original application, supplement, or resubmission.

(Comment 42) One comment stated that it would be unfair in most cases to expect us to meet the goal date for review of an application if a major amendment was submitted for a completely new indication in the middle of the initial review cycle. However, the comment stated that sometimes we request additional data or safety updates, which can lead to the expansion or modification of an indication (e.g., submission of long-term

safety data supporting chronic use). The comment added that there might be a significant public health reason to allow the submission of a major amendment to support a new indication. Therefore, the comment recommended that § 314.60(b)(6) be modified to allow exceptions when data to support a new or expanded indication are either requested by us or submitted with our prior concurrence.

(Response) We agree with the comment that it is appropriate to allow a major amendment to include data to support a slightly modified indication (e.g., increasing or decreasing the age range, increasing the severity of the disease) but not a completely new indication, regardless of whether the data supporting the new indication were submitted at the applicant's initiative or at our request. Therefore, we have revised § 314.60(b)(6) to state as follows: "A major amendment may not include data to support an indication or claim that was not included in the original application, supplement, or resubmission, but it may include data to support a minor modification of an indication or claim that was included in the original application, supplement, or resubmission." In addition, for the reasons stated in section III.B.3 of this document regarding § 314.3, we are substituting the phrase "indication or claim" for "indication for a use."

H. Amendments to ANDAs (Proposed § 314.96)

Proposed § 314.96(a)(2) stated that submission of an amendment containing significant data or information before the end of the initial review cycle constitutes an agreement between FDA and the applicant to extend the initial review cycle only for the time necessary to review the significant data or information and for no more than 180 days.

(Comment 43) One comment objected to proposed § 314.96(a)(2) and recommended several changes. First, the comment stated that it appeared that the only proposed change to § 314.96 was the removal of the condition that the cycle will be extended only for the time necessary to review the data. The comment maintained that this was not consistent with the intent to reduce ANDA approval times as stated in the ANDA amendments guidance. Second, the comment stated that § 314.96(a)(2) does not provide a definition of "significant." The comment recommended that the term "major amendment" be substituted for "amendment containing significant data or information" in § 314.96(a)(2). Third, the comment stated that § 314.96 lacks a provision regarding the submission of an amendment that contains data or information not considered significant. Finally, the comment stated that, in contrast to the provisions on major and nonmajor amendments to NDAs in § 314.60, it appeared that any amendment of an ANDA submitted at any time during the initial cycle constitutes an

agreement to extend the review cycle by 6 months. The comment maintained that the provisions on NDA amendments that take into consideration the timing and content of amendments were fair and appropriate and recommended that a similar approach be taken with ANDA amendments. To address all of these concerns, the comment recommended that § 314.96 be revised to state as follows: "The submission of a major amendment to an original ANDA at any time within the initial review cycle constitutes an agreement between the FDA and the applicant to extend the cycle only by the time necessary to review the data, and for no more than 180 days. A major amendment is defined as any new or revised information or data that, if it were to be submitted post-approval, would be categorized as a Prior Approval Supplement as defined in 314.70(b). The submission of a minor amendment to an original ANDA within 3 months of the end of the initial review cycle constitutes an agreement between the FDA and the applicant to extend the cycle by 30 to 60 days. The submission of a minor amendment more than 3 months before the close of the initial review cycle would not extend the review cycle. A minor amendment is defined as any new or revised information that, if it were to be submitted post-approval, would be categorized as a Changes Being Effectuated or Changes Being Effectuated in 30 Days supplement as defined in 314.70(c)."

(Response) Contrary to the comment, revised § 314.96(a)(2) retains the provision in previous § 314.96(a)(2) that the submission of an amendment to an ANDA containing significant data or information before the end of the review cycle constitutes an agreement to extend the review cycle "only for the time necessary to review the significant data or information and for no more than 180 days."

We do not agree with the comment's recommended changes to § 314.96. We do not believe that it is necessary to add a definition of major amendment in § 314.96. The ANDA amendments guidance does not provide a definition of major amendment but provides a listing of types of amendments that we regard as major amendments. These include, but are not limited to, amendments relating to the manufacture of a new batch of drug product, a new bioequivalence study that is unrelated to the manufacture of a new batch of the drug product, and new analytical methods and validation data. We believe that the guidance provides adequate information to applicants about the types of amendments that we regard as "containing significant data or information" under § 314.96(a)(2). We do not agree with the comment's suggested definition of major amendment because the matters that are the subject of supplements submitted under § 314.70 do not necessarily correlate with matters that are the subject of amendments submitted under § 314.96, and the regulatory

environment in which we review supplements differs from that in which we review amendments (e.g., we have much more information about a drug product after approval than we do before approval). For these reasons, we conclude that it is appropriate to retain the flexibility provided in § 314.96(a)(2) concerning what constitutes an amendment containing significant data or other information.

We also do not believe that it is necessary to include provisions on "minor" amendments to ANDAs in § 314.96. The ANDA amendments guidance states that, except for those amendments that are classified as "major" or "telephone," amendments will be designated as "minor," and the guidance provides examples of minor amendments (e.g., deficiencies in a drug master file, problems regarding good manufacturing practices). (According to the guidance, an amendment can be classified as a "telephone" amendment at the agency's discretion if the amendment would otherwise be classified as "minor" but the deficiencies are of a limited number or complexity (e.g., a need for clarification of data already submitted, a request for a postapproval commitment).) The guidance states that we attempt to review minor amendments within 30 to 60 days but notes that we cannot review all of these amendments within 60 days. We believe that the comment's proposed definition of minor amendment is not appropriate for the reasons we stated for not adopting the

proposed definition of major amendment. In addition, we decline to adopt the specific provisions on minor amendments suggested by the comment. The regulations in previous § 314.94 on amendments to pending ANDAs did not address minor amendments and did not parallel the provisions in § 314.60 on NDA amendments. Because ANDA amendments often differ in subject matter from NDA amendments, we do not believe it is necessary that the provisions on the content and timing of ANDA amendments match those for NDA amendments. We believe that the ANDA amendments guidance provides adequate information to ANDA applicants on minor amendments, and we do not find it necessary to codify our policy in the regulations at this time.

#### IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is not a significant regulatory action under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because our economic analysis and comments submitted in response to the proposed rule show that the provisions of this final rule either codify existing practice or bring about changes that impose no significant burdens, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$127 million, using the most current (2006) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

#### A. Impact of the Final Rule

As described in sections II and III of this document, the final rule makes the following changes: (1) For NDAs and ANDAs, replaces the two types of action letters currently used (approvable and not approvable letters) with complete response

letters; (2) for BLAs, incorporates into the regulations an existing policy on complete response letters; (3) incorporates into the regulations the terminology and procedures used in the user fee performance goals regarding NDA resubmissions; and (4) revises regulations governing extension of the initial review cycle in response to major amendments to unapproved applications, supplements, and resubmissions. For NDAs (with respect to resubmissions and amendments) and BLAs, the final rule codifies current agency practices. For ANDAs, the final rule revises regulations to be consistent with current practice or, where appropriate, with the provisions governing NDAs. The most significant impact of the final rule is on efficacy supplements to approved NDAs and on resubmissions of applications and efficacy supplements. The impact of specific provisions of the final rule on NDAs, ANDAs, efficacy supplements, manufacturing supplements, and resubmissions is described in greater detail in the following paragraphs.

#### 1. Complete Response Letter

We are amending our regulations to replace approvable and not approvable letters with complete response letters. Both approvable and not approvable letters indicated that an NDA or ANDA was not approvable in its current form, and that changes were necessary or that we required additional information. A complete response letter describes the deficiencies in an NDA or

ANDA and, when possible, recommends actions that the applicant might take to place the application in condition for approval. In the past, some drug manufacturers expressed concern that a not approvable letter sent an unintended message that a marketing application would never be approved, which could adversely affect a company's ability to raise capital. Thus, in addition to allowing us to meet our commitments under the user fee performance goals, this regulatory change addresses industry comments by adopting a more neutral mechanism to convey that an NDA or ANDA cannot be approved in its current form. (We had already adopted a policy of issuing complete response letters for BLAs, and the final rule simply codifies this policy.) Because this regulatory change is primarily administrative in nature and is being made in response to the user fee performance goals, it is expected to have little or no economic impact.

## 2. Resubmissions

We also are making regulatory changes to implement the user fee performance goals and to codify new terminology associated with the resubmission of drug marketing applications. A Class 2 resubmission--incorporating major changes or a significant amount of additional data--would start a new 6-month review cycle, whereas a Class 1 resubmission--incorporating minor changes or a limited amount of additional data--would begin a new 2-month

review cycle. These changes will codify agency practices regarding NDA resubmissions in place since 1998.

We are applying the Class 1 and Class 2 provisions to resubmissions of efficacy supplements as well. We agreed to make this policy change in PDUFA III because efficacy supplements, like original NDAs, contain varying amounts of data requiring different review times. We began to implement this change in October 2002. The application of the Class 1 and Class 2 provisions to resubmissions of efficacy supplements represents a regulatory change because under PDUFA II, all resubmissions of efficacy supplements would start a new 6-month review cycle. Under the final rule, a Class 1 resubmission of an efficacy supplement will extend the review cycle by only 2 months, rather than 6 months as occurred under PDUFA II. Review times for Class 2 efficacy supplement resubmissions will be largely unaffected by this change. Based on data from 1996 to 2000 (the most recent 5-year period for which complete data were available), an average of 16 efficacy supplements (approximately 40 percent) resubmitted annually would be reviewed in 2 months rather than the current 6 months. The final rule generally maintains current agency practice with respect to the review of other types of NDA supplements, i.e., for chemistry, manufacturing, or labeling changes. For ANDA resubmissions, the rule codifies the current practice of 6-month review.

### 3. Amendments to Unapproved Drug Marketing Applications

We also are revising our regulations on extending the initial review cycle following the submission of an amendment to an unapproved drug marketing application. The previous regulations stated that, for unapproved NDAs and efficacy supplements, submission of a major amendment extended the review cycle for the amount of time necessary to review the new information but not by more than 180 days. The final rule generally extends the review cycle by 3 months if a major amendment to an application, efficacy supplement, or resubmission of an application or efficacy supplement is submitted within 3 months of the end of the initial review cycle. (The final rule states that we may defer review until a subsequent review cycle.) If a major amendment is submitted more than 3 months before the end of the initial review cycle, the review cycle will not be extended (but FDA, in its discretion, may review the amendment during the initial review cycle or defer it until the subsequent review cycle). These changes codify the practice for NDAs that has been in place since 1998. However, we have only recently begun to apply this policy to efficacy supplements. Before October 2002, under the user fee performance goals, we did not extend the review cycle for a major amendment to an efficacy supplement. Therefore, as with the change regarding resubmissions of efficacy supplements, we believe that it is

appropriate to treat the change regarding amendments to unapproved efficacy supplements as a regulatory change for purposes of this analysis.

These provisions of the final rule might slightly increase review times for efficacy supplements for which at least one major amendment was received within 3 months of the end of the initial review cycle. Based on data from 1996 to 2000, these regulatory changes could affect as many as 11 percent of all efficacy supplements filed, or an average of 15 per year. The effect of this change is dependent on the timing of future filings and the number of instances in which we exercise our review discretion.

The final rule also codifies our practice of extending the initial review cycle for a manufacturing supplement by 2 months when a major amendment is submitted within 2 months of the end of the initial review cycle. As with major amendments to efficacy supplements, before October 2002, we did not extend the review cycle for a major amendment for a manufacturing supplement, so we are treating this codification as a regulatory change.

This change regarding manufacturing supplements might slightly increase review times for these supplements for which at least one major amendment was received within 2 months of the end of the initial review cycle. Based on data from 1996 to 2000, this regulatory change could affect as many as 6 percent of all

manufacturing supplements filed, or an average of 76 per year. The effect of this change is dependent on the timing of future filings and the number of instances in which we exercise our review discretion.

With respect to amendments to ANDAs, the changes to the regulations codify our current approach.

#### B. Summary of Impacts

Based on the preceding analysis, the changes to provisions governing resubmissions could result in reduced review times for up to 40 percent of efficacy supplements resubmitted annually. However, the provisions governing major amendments could slightly increase review times for up to 11 percent of efficacy supplements and 6 percent of manufacturing supplements (for which at least one major amendment was received during the initial review cycle) filed annually. The full impact of this rule would be affected by the number of future submissions and the extent to which we exercise our discretion to defer review until the next cycle. ANDAs will not be significantly affected by the changes to regulations.

#### C. Comments

We received one comment on the analysis of economic impacts in the proposed rule. The comment noted that we did not perform a cost-benefit analysis because the proposed rule was not expected to cause expenditure of \$100 million or more. The

comment stated that this would be a concern only if the rule brought about negative implications, but the comment stated that, if anything, the rule will bring economic enhancement. The comment maintained that: (1) More meaningful and direct communications will allow companies to market drugs and vaccines better; (2) the time to marketing might be shortened; and (3) more efficient application procedures will help companies optimize their earnings goals.

We agree with the comment that the rule will not have a negative economic impact on applicants seeking approval of drug and biological products.

#### D. Conclusion

Because this final rule generally amends previous regulations governing applications for approval to market new drugs and generic drugs to reflect user fee terminology and performance goals that have already been incorporated into FDA policies (except with respect to complete response letters, as noted above), we certify that the rule will not have a significant economic impact on a substantial number of small entities. Therefore, no further analysis is required under the Regulatory Flexibility Act.

#### V. Environmental Impact

We have determined under 21 CFR 25.30(h) that this action is of a class of actions that do not individually or cumulatively

have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### VI. Paperwork Reduction Act of 1995

This final rule does not contain new information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520). The final rule substitutes complete response letters for approvable and not approvable letters (in previous §§ 314.110 and 314.120, respectively) when we take action on marketing applications. The final rule retains the provisions requiring the recipient of the action letter (a complete response letter under the final rule) to amend the application (i.e., resubmit it), withdraw it, or ask us to provide an opportunity for a hearing on whether there are grounds for denying approval of the application. The final rule also revises the regulations (§§ 314.60, 314.96, 314.110, and 314.120) on extending the review cycle due to the submission of amendments before we issue an action letter and due to resubmissions, but does not change the information required in such amendments and resubmissions. OMB already has approved the information collection discussed earlier concerning responses to action letters under OMB control number 0910-0001, which expires on May 31, 2011.

The final rule also establishes regulations on the issuance of complete response letters to biologics license applicants and supplement applicants. The final rule codifies current agency practice on the issuance of complete response letters to these applicants and on applicant actions in response to these letters (resubmission or withdrawal of the application or supplement). OMB has already approved the information collection concerning responses to complete response letters for BLAs and BLA supplements under OMB control number 0910-0338, which expires on June 30, 2010.

We conclude that this final rule contains no new collection of information. Therefore, OMB clearance under the PRA is not required.

#### VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we have concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

List of Subjects

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 312, 314, 600, and 601 are amended as follows:

PART 312--INVESTIGATIONAL NEW DRUG APPLICATION

1. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 371, 381, 382, 383, 393; 42 U.S.C. 262.

2. Section 312.84 is amended in paragraph (c) by revising the first sentence to read as follows:

§ 312.84 Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses.

\* \* \* \* \*

(c) If FDA concludes that the data presented are not sufficient for marketing approval, FDA will issue a complete response letter under § 314.110 of this chapter or the biological product licensing procedures. \* \* \*

\* \* \* \* \*

PART 314--APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

3. The authority citation for 21 CFR part 314 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 356a, 356b, 356c, 371, 374, 379e.

4. Section 314.3 is amended in paragraph (b) by removing the definitions for "Approvable letter" and "Not approvable letter" and by adding the following definitions in alphabetical order:

§ 314.3 Definitions

\* \* \* \* \*

(b) \* \* \*

Class 1 resubmission means the resubmission of an application or efficacy supplement, following receipt of a complete response letter, that contains one or more of the

following: Final printed labeling, draft labeling, certain safety updates, stability updates to support provisional or final dating periods, commitments to perform postmarketing studies (including proposals for such studies), assay validation data, final release testing on the last lots used to support approval, minor reanalyses of previously submitted data, and other comparatively minor information.

Class 2 resubmission means the resubmission of an application or efficacy supplement, following receipt of a complete response letter, that includes any item not specified in the definition of "Class 1 resubmission," including any item that would require presentation to an advisory committee.

Complete response letter means a written communication to an applicant from FDA usually describing all of the deficiencies that the agency has identified in an application or abbreviated application that must be satisfactorily addressed before it can be approved.

\* \* \* \* \*

Efficacy supplement means a supplement to an approved application proposing to make one or more related changes from among the following changes to product labeling:

- (1) Add or modify an indication or claim;
- (2) Revise the dose or dose regimen;
- (3) Provide for a new route of administration;

(4) Make a comparative efficacy claim naming another drug product;

(5) Significantly alter the intended patient population;

(6) Change the marketing status from prescription to over-the-counter use;

(7) Provide for, or provide evidence of effectiveness necessary for, the traditional approval of a product originally approved under subpart H of part 314; or

(8) Incorporate other information based on at least one adequate and well-controlled clinical study.

\* \* \* \* \*

Original application means a pending application for which FDA has never issued a complete response letter or approval letter, or an application that was submitted again after FDA had refused to file it or after it was withdrawn without being approved.

\* \* \* \* \*

Resubmission means submission by the applicant of all materials needed to fully address all deficiencies identified in the complete response letter. An application or abbreviated application for which FDA issued a complete response letter, but which was withdrawn before approval and later submitted again, is not a resubmission.

\* \* \* \* \*

## § 314.50 [Amended]

5. Section 314.50 is amended in paragraph (d)(5)(vi)(b) in the fourth sentence by removing the phrase "following receipt of an approvable letter" and by adding in its place the phrase "in a resubmission following receipt of a complete response letter".

6. Section 314.60 is amended as follows:

- a. By revising the section heading;
- b. By revising paragraph (a);
- c. By redesignating paragraphs (b) and (c) as paragraphs (c) and (d), respectively;
- d. By adding new paragraph (b); and
- e. By revising newly redesignated paragraphs (c)(1)(iii) and (c)(1)(iv), and the first sentence of paragraph (c)(2), to read as follows:

§ 314.60 Amendments to an unapproved application, supplement, or resubmission.

(a) FDA generally assumes that when an original application, supplement to an approved application, or resubmission of an application or supplement is submitted to the agency for review, the applicant believes that the agency can approve the application, supplement, or resubmission as submitted. However, the applicant may submit an amendment to an application that has been filed under § 314.101 but is not yet approved.

(b)(1) Submission of a major amendment to an original application, efficacy supplement, or resubmission of an application or efficacy supplement within 3 months of the end of the initial review cycle constitutes an agreement by the applicant under section 505(c) of the act to extend the initial review cycle by 3 months. (For references to a resubmission of an application or efficacy supplement in paragraph (b) of this section, the timeframe for reviewing the resubmission is the "review cycle" rather than the "initial review cycle.") FDA may instead defer review of the amendment until the subsequent review cycle. If the agency extends the initial review cycle for an original application, efficacy supplement, or resubmission under this paragraph, the division responsible for reviewing the application, supplement, or resubmission will notify the applicant of the extension. The initial review cycle for an original application, efficacy supplement, or resubmission of an application or efficacy supplement may be extended only once due to submission of a major amendment. FDA may, at its discretion, review any subsequent major amendment during the initial review cycle (as extended) or defer review until the subsequent review cycle.

(2) Submission of a major amendment to an original application, efficacy supplement, or resubmission of an application or efficacy supplement more than 3 months before the

end of the initial review cycle will not extend the cycle. FDA may, at its discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

(3) Submission of an amendment to an original application, efficacy supplement, or resubmission of an application or efficacy supplement that is not a major amendment will not extend the initial review cycle. FDA may, at its discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

(4) Submission of a major amendment to a manufacturing supplement within 2 months of the end of the initial review cycle constitutes an agreement by the applicant under section 505(c) of the act to extend the initial review cycle by 2 months. FDA may instead defer review of the amendment until the subsequent review cycle. If the agency extends the initial review cycle for a manufacturing supplement under this paragraph, the division responsible for reviewing the supplement will notify the applicant of the extension. The initial review cycle for a manufacturing supplement may be extended only once due to submission of a major amendment. FDA may, at its discretion, review any subsequent major amendment during the initial review cycle (as extended) or defer review until the subsequent review cycle.

(5) Submission of an amendment to a supplement other than an efficacy or manufacturing supplement will not extend the initial review cycle. FDA may, at its discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

(6) A major amendment may not include data to support an indication or claim that was not included in the original application, supplement, or resubmission, but it may include data to support a minor modification of an indication or claim that was included in the original application, supplement, or resubmission.

(7) When FDA defers review of an amendment until the subsequent review cycle, the agency will notify the applicant of the deferral in the complete response letter sent to the applicant under § 314.110 of this part.

(c)(1) \* \* \*

(iii) The applicant has not obtained a right of reference to the investigation described in paragraph (c)(1)(ii) of this section; and

(iv) The report of the investigation described in paragraph (c)(1)(ii) of this section would be essential to the approval of the unapproved application.

(2) The submission of an amendment described in paragraph (c)(1) of this section will cause the unapproved application to be deemed to be withdrawn by the applicant under § 314.65 on the date of receipt by FDA of the amendment. \* \* \*

\* \* \* \* \*

7. Section 314.65 is amended by revising the second sentence to read as follows:

§ 314.65 Withdrawal by the applicant of an unapproved application.

\* \* \* If, by the time it receives such notice, the agency has identified any deficiencies in the application, we will list such deficiencies in the letter we send the applicant acknowledging the withdrawal. \* \* \*

§ 314.71 [Amended]

8. Section 314.71 is amended in paragraph (c) by adding the phrase "except as specified otherwise in this part" at the end of the sentence.

9. Section 314.96 is amended by revising paragraph (a)(2) and by removing paragraph (a)(3) to read as follows:

§ 314.96 Amendments to an unapproved abbreviated application.

(a) \* \* \*

(2) Submission of an amendment containing significant data or information before the end of the initial review cycle constitutes an agreement between FDA and the applicant to extend

the initial review cycle only for the time necessary to review the significant data or information and for no more than 180 days.

\* \* \* \* \*

10. Section 314.100 is revised to read as follows:

§ 314.100 Timeframes for reviewing applications and abbreviated applications.

(a) Except as provided in paragraph (c) of this section, within 180 days of receipt of an application for a new drug under section 505(b) of the act or an abbreviated application for a new drug under section 505(j) of the act, FDA will review it and send the applicant either an approval letter under § 314.105 or a complete response letter under § 314.110. This 180-day period is called the "initial review cycle."

(b) At any time before approval, an applicant may withdraw an application under § 314.65 or an abbreviated application under § 314.99 and later submit it again for consideration.

(c) The initial review cycle may be adjusted by mutual agreement between FDA and an applicant or as provided in §§ 314.60 and 314.96, as the result of a major amendment.

11. Section 314.101 is amended by revising paragraph (f)(1)(ii) and by revising the last sentence of paragraph (f)(2) to read as follows:

§ 314.101 Filing an application and receiving an abbreviated new drug application.

\* \* \* \* \*

(f) (1) \* \* \*

(ii) Issue a notice of opportunity for a hearing if the applicant asked FDA to provide it an opportunity for a hearing on an application in response to a complete response letter.

(2) \* \* \* If FDA disapproves the abbreviated new drug application, FDA will issue a notice of opportunity for hearing if the applicant asked FDA to provide it an opportunity for a hearing on an abbreviated new drug application in response to a complete response letter.

\* \* \* \* \*

12. Section 314.102 is amended in the last sentence in paragraph (b) by removing the phrase "an action" and adding in its place the phrase "a complete response" and by revising paragraph (d) to read as follows:

§ 314.102 Communications between FDA and applicants.

\* \* \* \* \*

(d) End-of-review conference. At the conclusion of FDA's review of an NDA as designated by the issuance of a complete response letter, FDA will provide the applicant with an opportunity to meet with agency reviewing officials. The purpose of the meeting will be to discuss what further steps need to be

taken by the applicant before the application can be approved. Requests for such meetings must be directed to the director of the division responsible for reviewing the application.

\* \* \* \* \*

§ 314.103 [Amended]

13. Section 314.103 is amended in paragraph (c)(1) in the first sentence by removing the phrase "an approvable or not approvable" and adding in its place the phrase "a complete response" and by removing the phrase "or § 314.120, respectively".

§ 314.105 [Amended]

14. Section 314.105 is amended in paragraph (b) in the first sentence by removing the phrase "(rather than an approvable letter under § 314.110)".

15. Section 314.107 is amended by adding a new sentence at the beginning of paragraph (b)(3)(v) to read as follows:

§ 314.107 Effective date of approval of a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act.

\* \* \* \* \*

(b) \* \* \*

(3) \* \* \*

(v) FDA will issue a tentative approval letter when tentative approval is appropriate in accordance with paragraph (b)(3) of this section. \* \* \*

\* \* \* \* \*

16. Section 314.110 is revised to read as follows:

§ 314.110 Complete response letter to the applicant.

(a) Complete response letter. FDA will send the applicant a complete response letter if the agency determines that we will not approve the application or abbreviated application in its present form for one or more of the reasons given in § 314.125 or § 314.127, respectively.

(1) Description of specific deficiencies. A complete response letter will describe all of the specific deficiencies that the agency has identified in an application or abbreviated application, except as stated in paragraph (a)(3) of this section.

(2) Complete review of data. A complete response letter reflects FDA's complete review of the data submitted in an original application or abbreviated application (or, where appropriate, a resubmission) and any amendments that the agency has reviewed. The complete response letter will identify any amendments that the agency has not yet reviewed.

(3) Inadequate data. If FDA determines, after an application is filed or an abbreviated application is received,

that the data submitted are inadequate to support approval, the agency might issue a complete response letter without first conducting required inspections and/or reviewing proposed product labeling.

(4) Recommendation of actions for approval. When possible, a complete response letter will recommend actions that the applicant might take to place the application or abbreviated application in condition for approval.

(b) Applicant actions. After receiving a complete response letter, the applicant must take one of following actions:

(1) Resubmission. Resubmit the application or abbreviated application, addressing all deficiencies identified in the complete response letter.

(i) A resubmission of an application or efficacy supplement that FDA classifies as a Class 1 resubmission constitutes an agreement by the applicant to start a new 2-month review cycle beginning on the date FDA receives the resubmission.

(ii) A resubmission of an application or efficacy supplement that FDA classifies as a Class 2 resubmission constitutes an agreement by the applicant to start a new 6-month review cycle beginning on the date FDA receives the resubmission.

(iii) A resubmission of an NDA supplement other than an efficacy supplement constitutes an agreement by the applicant to start a new review cycle the same length as the initial review

cycle for the supplement (excluding any extension due to a major amendment of the initial supplement), beginning on the date FDA receives the resubmission.

(iv) A major resubmission of an abbreviated application constitutes an agreement by the applicant to start a new 6-month review cycle beginning on the date FDA receives the resubmission.

(v) A minor resubmission of an abbreviated application constitutes an agreement by the applicant to start a new review cycle beginning on the date FDA receives the resubmission.

(2) Withdrawal. Withdraw the application or abbreviated application. A decision to withdraw an application or abbreviated application is without prejudice to a subsequent submission.

(3) Request opportunity for hearing. Ask the agency to provide the applicant an opportunity for a hearing on the question of whether there are grounds for denying approval of the application or abbreviated application under section 505(d) or (j)(4) of the act, respectively. The applicant must submit the request to the Associate Director for Policy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993. Within 60 days of the date of the request for an opportunity for a hearing, or within a different time period to which FDA and the applicant agree, the agency will either approve the application or abbreviated

application under § 314.105, or refuse to approve the application under § 314.125 or abbreviated application under § 314.127 and give the applicant written notice of an opportunity for a hearing under § 314.200 and section 505(c)(1)(B) or (j)(5)(c) of the act on the question of whether there are grounds for denying approval of the application or abbreviated application under section 505(d) or (j)(4) of the act, respectively.

(c) Failure to take action. (1) An applicant agrees to extend the review period under section 505(c)(1) or (j)(5)(A) of the act until it takes any of the actions listed in paragraph (b) of this section. For an application or abbreviated application, FDA may consider an applicant's failure to take any of such actions within 1 year after issuance of a complete response letter to be a request by the applicant to withdraw the application, unless the applicant has requested an extension of time in which to resubmit the application. FDA will grant any reasonable request for such an extension. FDA may consider an applicant's failure to resubmit the application within the extended time period or to request an additional extension to be a request by the applicant to withdraw the application.

(2) If FDA considers an applicant's failure to take action in accordance with paragraph (c)(1) of this section to be a request to withdraw the application, the agency will notify the applicant in writing. The applicant will have 30 days from the

date of the notification to explain why the application should not be withdrawn and to request an extension of time in which to resubmit the application. FDA will grant any reasonable request for an extension. If the applicant does not respond to the notification within 30 days, the application will be deemed to be withdrawn.

§ 314.120 [Removed and Reserved]

17. Section 314.120 is removed and reserved.

§ 314.125 [Amended]

18. Section 314.125 is amended in paragraph (a)(1) by removing the phrase "an approvable or a not approvable" and adding in its place the phrase "a complete response", and by removing the phrase "or § 314.120".

§ 314.430 [Amended]

19. Section 314.430 is amended in paragraph (b) in the first sentence by removing the phrase "approvable letter is sent to the applicant under § 314.110" and adding in its place the phrase "approval letter is sent to the applicant under § 314.105 or tentative approval letter is sent to the applicant under § 314.107"; and by removing the last sentence.

20. Section 314.440 is amended as follows:

a. In paragraph (a)(1) by removing the phrase "Document and Records Section" and by adding in its place the phrase "Central Document Room";

b. In paragraph (a)(3) by removing the phrase "or § 314.120";

c. In the introductory text of paragraph (b) by removing the phrase "or § 314.120"; and

d. By revising paragraph (a)(2) to read as follows:  
§ 314.440 Addresses for applications and abbreviated applications.

(a) \* \* \*

(2) Except as provided in paragraph (a)(4) of this section, an abbreviated application under § 314.94, and amendments, supplements, and resubmissions should be directed to the Office of Generic Drugs (HFD-600), Center for Drug Evaluation and Research, Food and Drug Administration, Metro Park North II, 7500 Standish Place, rm. 150, Rockville, MD 20855. This includes items sent by parcel post or overnight courier service. Correspondence not associated with an abbreviated application should be addressed specifically to the intended office or division and to the person as follows: Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Attn: [insert name of person], Metro Park North II, HFD-[insert mail code of office or division], 7500 Standish Place, rm. 150, Rockville, MD 20855. The mail code for the Office of Generic Drugs is HFD-600, the mail codes for the Divisions of Chemistry I, II, and III are HFD-620, HFD-640, and

HFD-630, respectively, and the mail code for the Division of Bioequivalence is HFD-650.

\* \* \* \* \*

PART 600--BIOLOGICAL PRODUCTS: GENERAL

21. The authority citation for 21 CFR part 600 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa-25.

§ 600.3 [Amended]

22. Section 600.3 is amended by adding new paragraphs (ll) and (mm) to read as follows:

§ 600.3 Definitions.

\* \* \* \* \*

(ll) Complete response letter means a written communication to an applicant from FDA usually describing all of the deficiencies that the agency has identified in a biologics license application or supplement that must be satisfactorily addressed before it can be approved.

(mm) Resubmission means a submission by the biologics license applicant or supplement applicant of all materials needed to fully address all deficiencies identified in the complete response letter. A biologics license application or supplement for which FDA issued a complete response letter, but which was

withdrawn before approval and later submitted again, is not a resubmission.

PART 601--LICENSING

23. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: 15 U.S.C. 1451-1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c-360f, 360h-360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec. 122, Pub. L. 105-115, 111 Stat. 2322 (21 U.S.C. 355 note).

§ 601.3 [Added]

24. Section 601.3 is added to subpart A to read as follows:

§ 601.3 Complete response letter to the applicant.

(a) Complete response letter. The Food and Drug Administration will send the biologics license applicant or supplement applicant a complete response letter if the agency determines that it will not approve the biologics license application or supplement in its present form.

(1) Description of specific deficiencies. A complete response letter will describe all of the deficiencies that the agency has identified in a biologics license application or supplement, except as stated in paragraph (a)(2) of this section.

(2) Inadequate data. If FDA determines, after a biologics license application or supplement is filed, that the data submitted are inadequate to support approval, the agency might

issue a complete response letter without first conducting required inspections, testing submitted product lots, and/or reviewing proposed product labeling.

(3) Recommendation of actions for approval. When possible, a complete response letter will recommend actions that the applicant might take to place its biologics license application or supplement in condition for approval.

(b) Applicant actions. After receiving a complete response letter, the biologics license applicant or supplement applicant must take either of the following actions:

(1) Resubmission. Resubmit the application or supplement, addressing all deficiencies identified in the complete response letter.

(2) Withdrawal. Withdraw the application or supplement. A decision to withdraw the application or supplement is without prejudice to a subsequent submission.

(c) Failure to take action. (1) FDA may consider a biologics license applicant or supplement applicant's failure to either resubmit or withdraw the application or supplement within 1 year after issuance of a complete response letter to be a request by the applicant to withdraw the application or supplement, unless the applicant has requested an extension of time in which to resubmit the application or supplement. FDA will grant any reasonable request for such an extension. FDA may

consider an applicant's failure to resubmit the application or supplement within the extended time period or request an additional extension to be a request by the applicant to withdraw the application.

(2) If FDA considers an applicant's failure to take action in accordance with paragraph (c)(1) of this section to be a request to withdraw the application, the agency will notify the applicant in writing. The applicant will have 30 days from the date of the notification to explain why the application or supplement should not be withdrawn and to request an extension of time in which to resubmit the application or supplement. FDA will grant any reasonable request for an extension. If the applicant does not respond to the notification within 30 days, the application or supplement will be deemed to be withdrawn.

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Dated: June 26, 2008.

*Jeffrey Shuren*

Jeffrey Shuren,  
Associate Commissioner for Policy and Planning..

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**CERTIFIED TO BE A TRUE  
COPY OF THE ORIGINAL**

*Dawn P. Hawkins*