BILLING CODE 4810–33–C; 6210–01–C; 6714–01–C; 6720–01–C

Dated: July 14, 2004.

John D. Hawke, Jr.,

Comptroller of the Currency.

By order of the Board of Governors of the Federal Reserve System on July 6, 2004.

Robert deV. Frierson,

DeputySecretary of the Board.

Dated in Washington, DC, this 28 day of June, 2004.

By order of the Board of Directors.

Federal Deposit Insurance Corporation.

Valerie J. Best,

Assistant Executive Secretary.

Dated: June 24, 2004.

James E. Gilleran,

Director, Office of Thrift Supervision.

[FR Doc. 04–16401 Filed 7–19–04; 8:45 am]

BILLING CODE 4810–33–P; 6210–01–P; 6714–01–P; 6720–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 312, 314, 600, and 601

[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: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend our regulations on new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for approval to market new drugs and generic drugs. We propose to discontinue the use of approvable letters and not approvable letters when taking action on marketing applications. Instead, we intend to use complete response letters to indicate that the review cycle is complete and that the application is not ready for approval. We also are proposing to revise the regulations on extending the review cycle due to the submission of an amendment to an unapproved application and starting a new cycle after a resubmission following receipt of a complete response letter. In addition, we are proposing to add to the regulations on biologics license applications (BLAs) a provision 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 that address procedures and establish target timeframes for reviewing human drug applications.

DATES: Submit written or electronic comments by October 18, 2004. See section VIII of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: You may submit comments, identified by [Docket No. 2004N–0267], by any of the following methods:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web Site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.
- E-mail: *fdadockets@oc.fda.gov*. Include [Docket No. 2004N–0267] in the subject line of your e-mail message.
- Fax: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the agency name and [Docket No. 2004N–0267] for this rulemaking. All comments received will be posted without change to *http://www.fda.gov/dockets/ecomments*, including any personal information provided. For detailed instructions on submitting comments and additional information on the rulemaking process, see the ''Request for Comments'' heading in the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/dockets/ecomments* and/or the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

The Office of Management and Budget (OMB) is still experiencing significant delays in the regular mail, including first class and express mail, and messenger deliveries are not being accepted. To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: Fumie Yokota, Desk Officer for FDA, FAX: 202–395–6974.

FOR FURTHER INFORMATION CONTACT: Brian L. Pendleton, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–5523.

SUPPLEMENTARY INFORMATION:

I. Background

A. User Fee Performance Goals and Complete Response Letters

In conjunction with the Prescription Drug User Fee Act of 1992 (PDUFA) (Public Law 102–571), we committed to meet certain goals for reviewing and acting on human drug applications, as defined in section 735(1) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 379g(1)). For example, we promised that by September 30, 1997, we would review and act on at least 90 percent of standard NDAs within 12 months after the submission date (H. Rep. No. 895, 102d Cong., 2d. sess. 32 (1992) (letter from David A. Kessler, M.D., Commissioner of Food and Drugs, to Representatives John Dingell and Norman Lent, House Committee on Energy and Commerce (September 14, 1992))).

FDA's drug application review performance goals were revised 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''). The goals were further revised 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 the 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).

Under the user fee performance goals, the term ''review and act on'' is defined as the issuance of a complete action letter after the complete review of a complete application that we have accepted for filing (Goals Letter at 15). An action letter, if not an approval, states the specific deficiencies of the application, and where appropriate, the actions necessary to place the application in condition for approval (id.).

As part of the user fee performance goals (first in PDUFA II and again in PDUFA III), FDA's Center for Drug Evaluation and Research (CDER) and

Center for Biologics Evaluation and Research (CBER) agreed to revise their regulations and procedures to provide for the issuance of either an approval or a ''complete response'' action letter at the completion of the review cycle for an application (Goals Letter at 15). We are now proposing to revise our regulations on human drugs in part 314 (21 CFR part 314) to replace two types of action letters currently used, approvable letters (§ 314.110) and not approvable letters (§ 314.120), with complete response letters. Because there are no provisions on action letters in the biological product regulations in parts 600 through 680 (21 CFR parts 600 through 680), CBER had only to change their standard operating procedures to incorporate the use of a complete response letter at the end of a review cycle for a biological product. Although CBER has already done this, we are now proposing to add a regulation (proposed § 601.3) on the issuance of complete response letters concerning BLAs and BLA supplements.

In replacing approvable and not approvable letters with complete response letters, our intent is to adopt a consistent and more neutral mechanism to convey that we cannot approve a drug marketing application in its current form. Historically, FDA issued a not approvable letter when deficiencies were major (e.g., no adequate and well-controlled studies, failure to demonstrate effectiveness, and a major safety concern). However, the distinction between approvable and not approvable letters became somewhat blurred. For example, in some cases, the absence of a second study supporting the effectiveness of a proposed drug product for a particular indication might have led to a not approvable letter; in other cases, FDA might have issued an approvable letter stating the need for additional evidence. Thus, issuance of an approvable letter might mean that an application needed only minor changes, such as a revision of labeling, or much more substantial changes. In addition, we subsequently approved many applications for which we had first issued a not approvable letter. Issuance of complete response letters will ensure a consistent approach to informing sponsors of needed changes before we can approve an application, with no implication as to the ultimate approvability of the application.

We also intend to incorporate into the regulations for NDAs the terminology based on the user fee performance goals regarding Class 1 and Class 2 resubmissions. A ''Class 1 resubmission'' is defined for performance goal purposes as an application resubmitted after receipt of an approvable or not approvable letter that includes only certain items such as draft or final printed labeling, safety or stability updates, or other minor clarifying information. A ''Class 2 resubmission'' is one that addresses any other items, including any item that would require presentation to an advisory committee. A Class 1 resubmission has a performance goal of 2 months and a Class 2 resubmission has a performance goal of 6 months. In accordance with the user fee goals, we are proposing to apply this terminology to original NDAs as well as to efficacy supplements (supplements to approved applications to make certain significant changes to product labeling). As a result, efficacy supplements would be treated like original NDAs with regard to resubmissions. We are proposing to apply different rules to resubmissions of other types of NDA supplements.

B. ANDAs

Although the user fee performance goals do not apply to ANDAs, the current regulations regarding approvable and not approvable letters in §§ 314.110 and 314.120 apply to both NDAs and ANDAs (with a few exceptions). As a result, any proposed change to the regulations for NDAs must take into account the impact on ANDAs. Because we intend to change the regulations for NDAs and we believe that these changes make sense for other applications, we have decided to propose similar changes for ANDAs.

C. Amendments to Unapproved Applications

The PDUFA performance goals also state that a major amendment to an unapproved application submitted within 3 months of the goal date (i.e., the end of the initial review cycle) extends the goal date by 3 months. We are proposing to incorporate this provision into our regulations by revising § 314.60 on amendments to unapproved applications. In accordance with the user fee goals, we are proposing to apply this provision to efficacy supplements and resubmissions of applications and efficacy supplements as well, but not to ANDAs.

II. Highlights of the Proposed Rule

A. Complete Response Letters

In accordance with the PDUFA performance goals and in response to the concerns previously discussed, we are proposing to substitute complete response letters for approvable and not approvable letters at the completion of the review cycle for an NDA or ANDA. Under proposed § 314.110, we will send a complete response letter if we determine that we will not approve an application or abbreviated application in its present form. The complete response letter usually would describe all of the specific deficiencies in the application or abbreviated application. If we determine, 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.

Table 1 of this document summarizes the changes that we propose to make in substituting complete response letters for approvable and not approvable letters:

TABLE 1.—SUMMARY OF PROPOSED CHANGES REGARDING SUBSTITUTION OF COMPLETE RESPONSE LETTER FOR APPROVABLE AND NOT APPROVABLE LETTERS

Current Regulations	Proposed Regulations
Approvable Letter for NDA	*Complete Response Letter*
• States that NDA is basically approvable if certain issues are resolved.	• States that FDA will not approve NDA or ANDA in its present form.
• Indicates that NDA substantially meets requirements of part 314 (21 CFR part 314) and FDA can approve it if applicant submits additional information or agrees to specific conditions (e.g., labeling changes).	• Describes all specific deficiencies, except when issued without conducting required inspections or labeling review because data found to be inadequate to support approval.
Approvable Letter for ANDA	

TABLE 1.—SUMMARY OF PROPOSED CHANGES REGARDING SUBSTITUTION OF COMPLETE RESPONSE LETTER FOR APPROVABLE AND NOT APPROVABLE LETTERS—Continued

Current Regulations	Proposed Regulations
• Indicates that ANDA substantially meets requirements of part 314 and is approvable if minor deficiencies are corrected.	• Reflects complete review of data in NDA or ANDA as well as amendments for which review cycle was extended.
• Describes deficiencies and states when applicant must respond.	• Where appropriate, describes actions necessary to place NDA or ANDA in condition for approval.
Not Approvable Letter for NDA or ANDA	
• 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.	
• Describes deficiencies in NDA or ANDA.	

For products for which approval of a BLA is required for marketing, we are proposing to adopt a new regulation, § 601.3, stating that FDA will send a BLA a complete response letter if we determine that we will not approve the BLA or BLA supplement in its present form.

B. Resubmissions

We also propose to revise the current provisions in §§ 314.110 and 314.120 on extension of the review period due to resubmission of an NDA or ANDA after receipt of an approvable or not approvable letter (to be replaced by a complete response letter). We propose that a Class 2 resubmission of an NDA following receipt of a complete response letter would start a new 6-month review cycle, as is the case with an ''amendment'' following receipt of a not approvable letter under current § 314.120(a)(1). A Class 1 resubmission of an NDA following receipt of a complete response letter would start a new 2-month review cycle.

The proposed rules on Class 1 and Class 2 resubmissions would also apply to efficacy supplements to NDAs, in accordance with the user fee performance goals. We believe that this is appropriate because efficacy supplements, like original applications, contain varying amounts of data. Where extensive data requiring significant agency resources for review are provided, the current 6-month review cycle should apply. But as with some NDA resubmissions, it would be appropriate to consider some smaller resubmissions of efficacy supplements as Class 1 resubmissions. We propose to apply different rules and terminology to other types of NDA supplements, including supplements dealing with chemistry, manufacturing, and controls (CMC) and labeling supplements for which no clinical data are needed. For NDA supplements other than efficacy supplements, a resubmission would start a new 6-month review cycle.

A ''major'' resubmission of an ANDA following receipt of a complete response letter would start a new 6-month review cycle, as is the case with an ''amendment'' following receipt of a not approvable letter under current § 314.120(a)(1). A ''minor'' resubmission of an ANDA would start a new review cycle of an unspecified length; the period might last from 30 days to a few months, depending on the issues involved. Under the relevant current CDER guidance document, entitled ''Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications'' (December 2001), a minor resubmission usually would start a new review cycle of between 30 to 60 days.

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

TABLE 2.—SUMMARY OF PROPOSED CHANGES TO REGULATIONS REGARDING APPLICANT'S RESPONSE TO AGENCY ACTION LETTER (RESUBMISSIONS)

Current Regulations	Proposed Regulations
Applicant's Response to Approvable Letter or Not Approvable Letter for NDA (or NDA Supplement)	*NDA or ANDA Applicant's Response to Complete Response Letter*
Within 10 days of date of letter, NDA applicant must do one of following:	Review period is extended until applicant takes one of following actions:
• Amend application or notify FDA of intent to file amendment.	• Resubmit NDA or ANDA, addressing identified deficiencies.
• Withdraw application.	—Class 1 resubmission of NDA or efficacy supplement starts new, 2-month cycle
• Request opportunity for hearing.	—Class 2 resubmission of NDA or efficacy supplement starts new, 6-month cycle
• Agree to extend review period to decide which of above actions to take.	—Resubmission of NDA supplement other than efficacy supplement starts new, 6-month cycle
Response to Approvable Letter for ANDA (or ANDA Supplement)	
• Correct deficiencies by specified date or FDA will refuse to approve ANDA or ANDA supplement.	—Major resubmission of ANDA or ANDA supplement starts new, 6-month cycle

TABLE 2.—SUMMARY OF PROPOSED CHANGES TO REGULATIONS REGARDING APPLICANT'S RESPONSE TO AGENCY ACTION LETTER (RESUBMISSIONS)—Continued

Current Regulations	Proposed Regulations
• Request opportunity for hearing within 10 days.	—Minor resubmission of ANDA or ANDA supplement starts new cycle of variable length
Response to Not Approvable Letter for ANDA (or ANDA Supplement)	
• Same as for NDAs except that 10-day period does not apply (with exception of request for opportunity for hearing).	• Withdraw NDA or ANDA.
• FDA may regard failure to respond within 180 days as request to withdraw.	• Request opportunity for hearing.

These proposed changes with respect to NDAs are consistent with our user fee performance goals for resubmissions of human drug applications following receipt of an action letter. The proposed provisions for ANDAs are similar, although not identical, to those for NDAs.

C. Amendments to Unapproved Applications

In accordance with our user fee goals, we are proposing to revise our regulations on extending the review cycle following the submission of an amendment to an unapproved NDA. Under current § 314.60, the submission of a major amendment to an unapproved NDA (such as one that contains significant new data from a previously unreported study or detailed new analyses of earlier data) may extend the review period by up to 180 days. Under the user fee goals, a major amendment to an original NDA submitted within 3 months of the goal date extends the goal date by 3 months (Goals Letter at 15). Therefore, we propose to revise § 314.60 to state that submission of a major amendment to an original NDA within 3 months of the end of the initial review cycle constitutes an agreement to extend the review cycle by 3 months. The proposed regulation states that FDA may instead defer review of such an amendment until the subsequent review cycle.

Under the proposal, the submission of a major amendment to an NDA more than 3 months before the close of the initial review cycle, or the submission of a minor amendment during the initial review cycle, would not extend the review cycle. FDA might, at its discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle. This proposed change to § 314.60 would codify for all NDAs our current policy on extending the review cycle for amendments to unapproved NDAs that are subject to user fees.

Also in accordance with the user fee goals, we are proposing to revise the regulations to provide that submission of a major amendment to an efficacy supplement to an approved application within 3 months of the end of the initial review cycle constitutes an agreement to extend the review cycle for the supplement by 3 months (although we could defer review to the subsequent cycle). It is appropriate to treat major amendments to efficacy supplements the same way as major amendments to original applications because their review requires significant agency resources. Amendments to other types of NDA supplements, however, will not extend the review cycle.

An additional change that is consistent with the user fee goals would provide that the submission of a major amendment to a resubmission of an application or efficacy supplement within 3 months of the end of the initial review cycle constitutes an agreement to extend the review cycle by 3 months (again, we could elect to defer review). Because major amendments to these resubmissions generally require the review of substantial data, it is appropriate to treat them the same way as major amendments to original applications or efficacy supplements.

We propose to make only minor revisions to the regulations on submitting amendments to unapproved ANDAs in § 314.96. The proposed rule would clarify that an amendment to an ANDA submitted before the end of the initial review cycle that contains significant data or information could extend the initial review cycle by as many as 180 days.

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

TABLE 3.—SUMMARY OF PROPOSED CHANGES TO REGULATIONS ON AMENDMENTS SUBMITTED PRIOR TO ACTION LETTER

Current Regulations	Proposed Regulations
Amendments to Unapproved NDAs and NDA Supplements	*Amendments to Unapproved NDAs and Efficacy Supplements*
• Submission of major amendment constitutes agreement to extend deadline for FDA decision.	• Submission of major amendment within 3 months of end of initial review cycle constitutes agreement to extend cycle by 3 months; FDA may instead defer review to subsequent cycle.
• FDA may not extend review period more than 180 days.	• Initial review cycle may be extended only once for major amendment.
• Submission of nonmajor amendment will not extend review period.	• Submission of major amendment more than 3 months before end of initial review cycle will not extend cycle.
Amendments to Unapproved ANDAs and ANDA Supplements	• Submission of minor amendment will not extend review cycle.
• Submission of amendment containing significant data or information constitutes agreement to extend review period up to 180 days.	

TABLE 3.—SUMMARY OF PROPOSED CHANGES TO REGULATIONS ON AMENDMENTS SUBMITTED PRIOR TO ACTION LETTER—Continued

Current Regulations	Proposed Regulations
• Same for amendments to unapproved ANDA supplements.	
	Amendments to Unapproved NDA Supplements Other Than Efficacy Supplements
	• Submission of any amendment will not extend the initial review cycle.
	Amendments to Resubmissions of Applications and Efficacy Supplements
	• Submission of major amendment within 3 months of end of initial review cycle constitutes agreement to extend cycle by 3 months; FDA may instead defer review to subsequent cycle.
	Amendments to Unapproved ANDAs and ANDA Supplements
	• Unchanged

III. Description of the Proposed Rule

The proposed rule would make the following five types of revisions and additions to the regulations: (1) Revisions to remove the use of approvable and not approvable letters for NDAs and ANDAs and to incorporate the use of complete response letters and use of the term ''review cycle'', (2) addition of provisions on the issuance of complete response letters concerning BLAs and BLA supplements, (3) revisions related to resubmissions of NDAs and ANDAs after receipt of complete response letters, (4) miscellaneous technical revisions related to the use of complete response letters for NDAs and ANDAs, and (5) revisions related to amendments to unapproved NDAs and ANDAs.

A. The Complete Response Letter and the Review Cycle for NDAs and ANDAs

1. Definitions (Proposed § 314.3)

Current § 314.3(b) defines ''approvable letter'' and ''not approvable letter.'' We propose to revise § 314.3(b) by removing these definitions and adding a definition of ''complete response letter.'' A complete response letter would be defined 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. (Under current § 314.3, ''application'' refers to an NDA and ''abbreviated application'' refers to an ANDA.)

We also propose to revise § 314.3(b) by adding a definition of ''original application.'' An original application would be defined as a pending application for which we have never issued a complete response letter or approval letter or an application that was submitted again after we had refused to file it or after it was withdrawn without being approved.

We also propose to add definitions of ''Class 1 resubmission'' and ''Class 2 resubmission'' for resubmissions of NDAs. A ''Class 1 resubmission'' would be defined as the resubmission of an application (i.e., an NDA), 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.[1] A ''Class 2 resubmission'' would be defined as the resubmission of an application, 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. These definitions of Class 1 and Class 2 resubmissions of NDAs reflect those stated in the Goals Letter and will not be applied to ANDAs.

[1] This definition of Class 1 resubmission matches the definition stated in the user fee Goals Letter, except that the latter refers to ''other minor clarifying information'' and states that ''[o]ther specific items may be added later as the Agency gains experience with the scheme and will be communicated via guidance documents to industry'' (Goals Letter at 16). The proposed definition would allow resubmissions that contain unspecified information of a comparatively minor nature to be treated as Class 1 resubmissions. FDA might address specific types of such resubmissions in agency guidance.

In addition, we propose to revise § 314.3(b) to add a definition of ''efficacy supplement.'' An ''efficacy supplement'' would be defined as a supplement to an approved NDA 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 part 314, or (8) incorporate other information based on at least one adequate and well-controlled clinical study.

2. Timeframes for Review (Proposed § 314.100)

Current § 314.100 addresses the timeframes for reviewing applications and abbreviated applications. Section 314.100(a) states that within 180 days of receipt of an application for a new drug under section 505(b) of the act (21 U.S.C. 355(b)) or of 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, an approvable letter under § 314.110, or a not approvable letter under § 314.120. This 180-day period is called the review clock.

We propose to revise § 314.100(a) by creating two separate provisions reflecting different review cycles for applications that are subject to user fees and those that are not subject to such fees. Proposed § 314.100(a)(1) states that, except as provided in

§ 314.100(a)(2), within 180 days of receipt of an application for a new drug under section 505(b) of the act or of 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. We propose to rename this 180-day period the ''initial review cycle'' to be consistent with the term we currently use.

Proposed § 314.100(a)(2) states that, for applications that are human drug applications, as defined in section 735(1)(A) and (B) of the act (NDAs), 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 our user fee performance goals for reviewing such applications and supplements. We are making this change to reflect that, under the user fee performance goals, we are not expected to review and act on all applications that are subject to user fees within 180 days of receipt of such applications. Rather, we have committed to take action on certain percentages of applications within different time periods, depending on the type of application (e.g., standard, priority, supplement, resubmission) and the relevant fiscal year (see Goals Letter at 1, 2, and 3). In some cases, such as CMC supplements that require prior approval, we have committed to taking action in less than 180 days. Consequently, proposed § 314.100(a)(2) reflects that the initial review cycle for human drug applications and supplements to such applications may in some cases be shorter or longer than 180 days.

Current § 314.100(b) states that, during the review period, an applicant may withdraw an application under § 314.65 or an abbreviated application under § 314.99 and later resubmit it. We will treat the subsequent submission as a new original application or abbreviated application. Current § 314.100(b) uses the term ''review period'' rather than ''review clock'' because it is intended to address withdrawals made at any time while an application or abbreviated application is pending before the agency (i.e., filed but not yet approved), not simply withdrawals made while the review clock is running. (Although not defined in the regulations, the ''review period'' means the period from filing of an NDA or receipt of an ANDA to the ultimate disposition of the application, either by approval, refusal to approve the NDA under § 314.125 or the ANDA under § 314.127, or withdrawal of the application.) Rather than use the term ''review period'' or ''review clock,'' we propose to clarify § 314.100(b) by stating that, 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. We propose to substitute the phrase ''submit it again'' for ''resubmit it'' because we want to limit the terms ''resubmit'' and ''resubmission'' in part 314 to resubmissions after receipt of a complete response letter.

Current § 314.100(c) states that the review clock may be extended by mutual agreement between FDA and an applicant or as provided in §§ 314.60 or 314.96, as the result of a major amendment. To be consistent with proposed § 314.100(a)(1), we propose to revise this provision by substituting ''initial review cycle'' for ''review clock.''

3. Filing an NDA and Receiving an ANDA (Proposed § 314.101)

Current § 314.101(f)(1) states that within 180 days after the date of filing of an NDA, 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 if the applicant asked FDA to provide it an opportunity for a hearing on an application in response to an approvable letter or a not approvable letter.

Consistent with our proposed revision of § 314.100(a), we are proposing to add a new § 314.101(f)(2) (redesignating current § 314.101(f)(2) and (f)(3) as § 314.101(f)(3) and (f)(4), respectively). The new section states that for applications that are human drug applications, as defined in section 735(1)(A) and (B) of the act, and supplements to such applications, as defined in section 735(2) of the act, the 180-day period specified in § 314.101(f)(1) will be adjusted to be consistent with the agency's user fee performance goals for reviewing such applications and supplements. We also propose to replace references in current § 314.101(f) to approvable and/or not approvable letters with references to complete response letters.

4. Approvable and Not Approvable Letters (Proposed §§ 314.110 and 314.120)

Current § 314.110 sets forth provisions on the issuance of and response to approvable letters. Section 314.110(a) states that it may be appropriate for FDA to issue an approvable letter at the end of a review period to inform an applicant that its application or abbreviated application is basically approvable if the applicant resolves certain issues. It also states that an approvable letter signifies that we believe that we can approve the application or abbreviated application if the applicant submits specific additional information or material or agrees to specific conditions (e.g., changes in labeling). Section 314.110(a) further states that as a practical matter, an approvable letter in most instances serves as a mechanism for resolving outstanding issues on drugs that are about to be approved and marketed.

Current § 314.120 addresses the agency's issuance of not approvable letters to applicants and applicants' responses to such letters. Section 314.120(a) states that we will send an applicant a not approvable letter if we believe that the application may not be approved for one of the reasons given in § 314.125, or that an abbreviated application may not be approved for one of the reasons given in § 314.127.

We propose to revise § 314.110 (and to remove and reserve § 314.120) by replacing references to approvable letters and not approvable letters with references to complete response letters.

a. *Issuance of complete response letters.* Proposed § 314.110 is entitled ''Complete response letter to the applicant.'' Proposed § 314.110(a) states that we will send the applicant a complete response letter if we determine 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.

Proposed § 314.110(a)(1) states that a complete response letter will describe all of the specific deficiencies in the application or abbreviated application, except as stated in proposed § 314.110(a)(3). (Under current procedures, we might also notify the applicant of deficiencies in certain parts of the application or abbreviated application before issuance of a complete response letter.)

Following issuance of a complete response letter, we would not expect to identify any additional deficiencies in an NDA or ANDA. However, it is possible that we might find additional deficiencies in an application following review of: (1) Data submitted in an amendment not reviewed before issuance of the complete response letter, (2) a resubmission containing new data or analyses, or (3) additional safety data obtained from any source. These additional deficiencies might be based wholly on the newly submitted data or might reflect new analyses of previous data prompted by the new data. Finally, it is also possible that we might find

additional deficiencies in previously reviewed data on the basis of advice from an advisory committee.

Proposed § 314.110(a)(2) states that the 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 for which the review cycle was extended. It adds that the complete response letter will identify any amendments for which the review cycle was not extended that we have not yet reviewed.

Proposed § 314.110(a)(3) states that if we determine, 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.

Proposed § 314.110(a)(4) states that, where appropriate, a complete response letter will describe the actions necessary to place the application or abbreviated application in condition for approval.

b. *Responses to complete response letters.* Current § 314.110(a) states that within 10 days after the date of an approvable letter, the sponsor of an NDA must respond in one of the following several ways: (1) Amend the application (or notify us of an intent to do so), (2) withdraw the application (failure to respond within 10 days to an approvable letter is regarded as a request to withdraw the application), (3) ask us to provide the applicant with an opportunity for a hearing on whether there are grounds for denying the approval of the application under section 505(d) of the act, or (4) notify us that the applicant agrees to extend the review period under section 505(c) of the act so that the applicant can determine whether to take one of the previously listed actions.

Current § 314.110(b) addresses the issuance of approvable letters to ANDA applicants. Under § 314.110(b), we will send an ANDA applicant an approvable letter only if the abbreviated application substantially meets the requirements of part 314 and we believe that we can approve it if minor deficiencies (e.g., regarding labeling) are corrected. The approvable letter describes the deficiencies in the ANDA and states a date by which the applicant must respond. Unless the applicant corrects the deficiencies within the specified period, FDA will refuse to approve the ANDA. Within 10 days of the date of the approvable letter, the applicant may request an opportunity for a hearing.

In proposed § 314.110(b), we direct both NDA and ANDA applicants to take one of three actions following receipt of a complete response letter, eliminating (except with respect to resubmissions) the separate provisions for ANDAs in current § 314.110(b). We also propose to delete the requirement that NDA applicants take action within 10 days.

The first option for the recipient of a complete response letter, stated in proposed § 314.110(b)(1), is to resubmit the application or abbreviated application, addressing all deficiencies identified in the letter. For purposes of § 314.110, a resubmission would mean the submission by an applicant of all materials needed to fully address all deficiencies identified in the complete response letter.

Under proposed § 314.110(b)(1)(i), a resubmission of an NDA or an efficacy supplement that we classify as a Class 1 resubmission would constitute an agreement by the applicant to start a new 2-month review cycle beginning on the date we receive the resubmission. Under proposed § 314.110(b)(1)(ii), a resubmission of an NDA or an efficacy supplement that we classify as a Class 2 resubmission would constitute an agreement by the applicant to start a new 6-month review cycle beginning on the date we receive the resubmission.

For NDA supplements other than efficacy supplements, such as a supplement for a change in CMC or a labeling supplement that does not require clinical data, we propose to retain the current practice of not applying the Class 1 and Class 2 terminology and review cycle lengths. Thus, 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.

For resubmissions of ANDAs, we propose to continue the current practice of categorizing them as ''major'' or ''minor.'' Under proposed § 314.110(b)(1)(iv), a major resubmission of an ANDA would constitute an agreement by the applicant to start a new 6-month review cycle beginning on the date we receive the resubmission. Under proposed § 314.110(b)(1)(v), a minor resubmission of an ANDA would constitute an agreement to start a new review cycle (length unspecified) beginning on the date we receive the resubmission. The actual length of the cycle would depend on the contents of the resubmission. As noted in section II.C of this document, CDER's guidance on ''Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications'' provides guidance on how the agency handles these resubmissions. The guidance states that CDER attempts to review most minor amendments within 30 to 60 days, and we intend to apply this to minor resubmissions of ANDAs. Under the proposed rule, resubmissions of supplements to approved ANDAs would continue to be treated the same as ANDA resubmissions in accordance with § 314.97.

The second option for the recipient of a complete response letter, stated in proposed § 314.110(b)(2), is to withdraw the application or abbreviated application. A decision to withdraw an application or abbreviated application would be without prejudice to a subsequent submission.

The third option for the recipient of a complete response letter, stated in proposed § 314.110(b)(3), is to ask us 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. Within 60 days of the date of a request for an opportunity for a hearing, or within a different time period to which we and the applicant agree, we would take either of the following actions: (1) Approve the application or abbreviated application under § 314.105 or (2) refuse to approve the NDA under § 314.125 or the ANDA 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.

Under proposed § 314.110(c), an applicant agrees to extend the review period under section 505(c)(1) of the act until it takes any of the actions listed in proposed § 314.110(b). Section 505(c)(1) of the act directs FDA, within 180 days after the filing of an application under section 505(b) of the act or an additional period agreed upon by the applicant and the agency, to either approve the application (if we find that none of the grounds for denying approval stated in section 505(d) of the act applies) or give the applicant an opportunity for a hearing under section 505(d) on the question of whether such application is approvable. Thus, the addition of the provision on agreement to extend the review period in proposed § 314.110(c) would ensure that, if we do not approve an application, the applicant is provided a notice of opportunity for a hearing within the time specified by section 505(c)(1) of the act.

Proposed § 314.110(c) further states that we may consider an NDA applicant's failure to take any of the actions listed in § 314.110(b) within 1 year after receiving a complete response letter to be a request by the applicant to withdraw the application. However, regarding ANDAs, proposed § 314.110(c) states that we may consider an applicant's failure to take any of the listed actions within 6 months after receiving a complete response letter to be a request by the applicant to withdraw the abbreviated application. We believe that the shorter time period for ANDAs is appropriate because an ANDA resubmission is not likely to involve generation of clinical data and deficiencies normally could be addressed within 6 months.

Because we propose to revise current § 314.110 to state the provisions on complete response letters, we propose to delete current § 314.120 on not approvable letters and to reserve this section for future use.

B. Complete Response Letter for BLAs

To incorporate into the biologics regulations the use of complete response letters for BLAs, we are proposing to add a definition of ''complete response letter'' to § 600.3 and to add § 601.3 on complete response letters.

1. Definition (Proposed § 600.3)

We propose to add to current § 600.3, paragraph (jj) to define a complete response letter. Under proposed § 600.3(jj), a complete response letter would be defined as a written communication to an applicant from FDA usually identifying all of the deficiencies in a biologics license application or supplement that must be satisfactorily addressed before it can be approved. (Current § 600.3(gg) defines a ''supplement'' as a request to the Director, Center for Biologics Evaluation and Research, to approve a change in an approved license application.)

2. Complete Response Letter to the Applicant (Proposed § 601.3)

To incorporate current CBER policy into the regulations, we are proposing to establish a new § 601.3 on complete response letters. Under proposed § 601.3(a), FDA will send the biologics license applicant or supplement applicant a complete response letter if we determine that we will not approve the biologics license application or supplement in its present form.

Under proposed § 601.3(b), a biologics license applicant or supplement applicant must take one of two actions after receiving a complete response letter. Under proposed § 601.3(b)(1), the license or supplement applicant may resubmit the application or supplement, addressing all deficiencies identified in the complete response letter. Under proposed § 601.3(b)(2), the license or supplement applicant may withdraw the application or supplement; a decision to withdraw would be without prejudice to a subsequent submission.

Finally, under proposed § 601.3(c), 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 receiving a complete response letter to be a request by the applicant to withdraw the application or supplement.

C. Miscellaneous Revisions Related to Adoption of Complete Response Letters for NDAs and ANDAs

To reflect FDA's use of complete response letters for NDAs and ANDAs, the agency proposes to make the following additional revisions to its regulations:

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

Current § 314.50 specifies the content and format of NDAs. Section 314.50(d) describes the technical sections required in each application. Section 314.50(d)(5)(vi)(b) states that an applicant periodically must update its pending application with new safety information that might affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. The applicant must file these safety update reports 4 months after the initial submission, after receiving an approvable letter, and when otherwise requested by FDA.

We propose to revise § 314.50(d)(5)(vi)(b) by replacing the requirement to submit a safety update report following receipt of an approvable letter with a requirement to submit a safety update report in a resubmission following receipt of a complete response letter. This would ensure that we have more extensive safety information than was available at the time of the original submission. In addition, we could, if appropriate, require submission of a safety update report immediately before issuing an approval letter under the current provision that allows us to require submission of a report ''at other times as requested by FDA.''

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

Current § 314.65 states that an applicant may at any time withdraw an application that is not yet approved by notifying us in writing. It further states that we will consider an applicant's failure to respond within 10 days to an approvable letter under § 314.110 or a not approvable letter under § 314.120 to be a request by the applicant to withdraw the application.

We propose to revise § 314.65 to delete the reference to responding within 10 days to an approvable or not approvable letter, consistent with proposed § 314.110. In addition, we propose to add a statement that if, by the time we receive a notice of withdrawal, we have identified any deficiencies in the application, we will list those deficiencies in the letter we send the applicant acknowledging the withdrawal.

3. Communications Between FDA and Applicants (Proposed § 314.102)

Current § 314.102 addresses communications between FDA and applicants. Section 314.102(b) states that FDA reviewers shall make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application or an abbreviated application when those deficiencies are discovered, particularly deficiencies concerning CMC issues. This early communication is intended to permit applicants to correct readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed. Section 314.102(b) further states that such early communication would not ordinarily apply to major scientific issues; instead, major scientific issues will ordinarily be addressed in an action letter.

We propose to revise § 314.102(b) to clarify that major scientific issues will ordinarily be addressed in a complete response letter, even though they may have been addressed earlier in a discipline review letter in accordance with user fee performance goals.

Current § 314.102(d) discusses end-of-review conferences. It states that at the conclusion of our review of an application or abbreviated application as designated by the issuance of an approvable or not approvable letter, we will provide applicants 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 or abbreviated application can be approved. Section 314.102(d) further states that this meeting will be available on all applications or abbreviated applications, with priority given to applications for new chemical entities and major new indications for marketed drugs and for the first duplicates for such drugs. Requests for such meetings must be directed to the director of the division responsible for reviewing the application or abbreviated application.

We propose to revise § 314.102(d) by replacing ''an approvable or not approvable letter'' with ''a complete response letter.'' In addition, we propose to delete the references to abbreviated applications because the Office of Generic Drugs, which reviews such applications, does not routinely provide end-of-review conferences for ANDAs. Finally, because we virtually always agree to requests for end-of-review conferences for NDAs and do not prioritize the scheduling of such conferences for particular types of NDAs, we propose to remove the reference to priority status for certain types of NDAs.

4. Approval (Proposed § 314.105)

Current § 314.105(b), concerning approval of applications and abbreviated applications, states that FDA will approve an application and issue the applicant an approval letter (rather than an approvable letter under § 314.110) on the basis of draft labeling if only minor labeling deficiencies remain. We propose to delete the reference to approvable letters. Substituting a reference to complete response letters would not be appropriate because issuance of such a letter would not necessarily signify that we believe that an application is basically approvable provided that certain issues are resolved or that the application substantially meets the requirements of part 314, as is the case with approvable letters issued under current § 314.110.

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

Current § 314.430(b) states that we will not publicly disclose the existence of an application or abbreviated application before we send an approvable letter to the applicant unless the existence of the application or abbreviated application has been previously publicly disclosed or acknowledged. The provision further states that CDER will maintain and make available for public disclosure a list of applications or abbreviated applications for which we have sent an approvable letter to the applicant.

We propose to revise § 314.430(b) to allow for FDA disclosure of the existence of an NDA or ANDA after issuance of an approval letter or tentative approval letter. Proposed § 314.430 (b) states that we will not publicly disclose the existence of an application or abbreviated application before we send the applicant an approval letter under § 314.105 or a tentative approval letter under § 314.107, unless the existence of the application or abbreviated application has been previously publicly disclosed or acknowledged. We do not believe that it is necessary to include a provision stating that the agency will maintain and make available for public disclosure a list of approved applications and abbreviated applications because we already make this information available by routinely announcing the approval of NDAs and ANDAs within days of their approval and publishing an annual list (with monthly supplements) of ''Approved Drug Products With Therapeutic Equivalence Evaluations'' (known as the ''Orange Book'').

We issue a tentative approval letter when an application meets the scientific and technical requirements for approval under section 505(b) or (j) of the act but marketing exclusivity (e.g., pediatric exclusivity, orphan drug exclusivity) or patent rights prevent final approval of the drug product. As stated in § 314.107(b)(3)(v), tentative approval of an application does not constitute an approval of an application and cannot, absent a final approval letter from the agency, result in an effective approval of an application. However, because we only issue tentative approval letters when an application has met the scientific and technical approval requirements, tentative approval letters do not present the same disclosure concerns as correspondence regarding other unapproved applications. Therefore, we intend to follow our past practice of acknowledging the existence of applications that have received tentative approval letters and making those letters publicly available.

Because current § 314.107(b)(3) does not explicitly refer to our practice of issuing a letter notifying an applicant of a tentative approval, we propose to revise § 314.107(b)(3)(v) to state that we will issue a tentative approval letter when tentative approval is appropriate in accordance with § 314.107 (b)(3).

The changes that we are proposing to the disclosure provisions would mean that FDA disclosure of the existence of an NDA or ANDA might result in later disclosure than sometimes occurs under the current regulation (i.e., with respect to those applications for which FDA now issues approvable letters). However, we believe that this effect would be limited because most applicants (at least for NDAs) publicly reveal the existence of their applications before agency issuance of an approval letter. Moreover, the proposed change would be consistent with the agency's long-standing presumption that, before approval (and absent evidence to the contrary), the existence of an application is confidential commercial information under 21 CFR 20.61. For example, under § 601.51, FDA will not disclose the existence of a biological product file before a BLA has been approved unless it has previously been publicly disclosed or acknowledged.

However, we specifically invite comment on whether it would be appropriate for FDA to disclose the existence of an NDA or ANDA following issuance of a complete response letter and if so, what conditions, if any, should be placed on such disclosure. For example, one alternative to the proposed approach would be that FDA would publicly disclose the existence of an NDA or ANDA following issuance of a complete response letter unless the applicant notified the agency (by some specified deadline) that the applicant had not publicly disclosed or acknowledged the existence of the application or abbreviated application. This approach would allow applicants to prevent agency disclosure of the existence of an application despite the issuance of a complete response letter. However, it also would create the potential for inadvertent disclosure and necessitate the establishment of a system to record and track applicants' positions regarding disclosure. This could be burdensome to applicants and the agency.

6. Other Technical Revisions (Proposed §§ 312.84, 314.103, 314.125, and 314.440)

We are proposing to revise other sections of the regulations to replace references to approvable and/or not approvable letters with references to complete response letters. These revisions would be made to § 312.84 (Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses), § 314.103 (Dispute resolution), § 314.125 (Refusal to approve an application), and § 314.440 (Addresses for applications and abbreviated applications). (The proposed rule also revises this section by providing the current address to

which an NDA must be submitted and the address for applications regarding certain products reviewed by CBER.)

D. Amendments to Unapproved NDAs, ANDAs, and Unapproved Supplements to Approved NDAs

The other principal purpose of this proposed rule, besides the adoption of complete response letters and related changes to resubmissions, is to revise the regulations in §§ 314.60 and 314.96 on amendments to unapproved NDAs and ANDAs, respectively.

1. Amendments to Unapproved NDAs, Supplements, and Resubmissions (Proposed § 314.60)

Amendments to unapproved NDAs are addressed in § 314.60. Current § 314.60(a) states that except as provided in § 314.60 (b), the applicant may submit an amendment to an application that is filed under § 314.100, but not yet approved. (The reference to § 314.100 is in error; § 314.101 not § 314.100 addresses the filing of applications.) Section 314.60(a) further states that the submission of a major amendment (e.g., one that contains significant new data from a previously unreported study or detailed new analyses of earlier data) constitutes an agreement by the applicant under section 505(c) of the act to extend the date by which we are required to decide on the application. The section adds that we ordinarily will extend the review period but only for the time needed to review the new information, and we may not extend the period for more than 180 days. If we extend the review period for the application, the director of the division responsible for reviewing the application will notify the applicant of the length of the extension. The submission of an amendment that is not a major amendment will not extend the review period.

We propose to revise § 314.60(a) to state that we generally assume that when an original application (i.e., original NDA) supplement to an approved application or resubmission of an application or supplement is submitted to the agency for review, the applicant believes that we can approve the application, supplement, or resubmission as submitted. However, the applicant may submit an amendment to an application or supplement that has been filed under § 314.101 but is not yet approved.

In place of the provisions in current § 314.60(a), we propose to add new § 314.60(b). 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 constitutes an agreement by the applicant under section 505(c) of the act to extend the review cycle by 3 months. However, the proposed regulation states that we may instead defer review of such an amendment until the subsequent review cycle. The subsequent review cycle would run from the resubmission of the application, efficacy supplement, or resubmission following receipt of the complete response letter to the issuance of either a second complete response letter or an approval letter. Under proposed § 314.60(b)(1), if we extend the initial review cycle for an original application, efficacy supplement, or resubmission of an application or efficacy supplement under this paragraph (b)(1), the division responsible for reviewing the application, supplement, or resubmission will notify the applicant of the extension. Proposed § 314.60(b)(1) further states 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 submission of a major amendment. Finally, proposed § 314.60(b)(1) states that 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.

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 will not extend the cycle. We may, at our discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

Under proposed § 314.60(b)(3), submission of a minor amendment to an original application, efficacy supplement, or resubmission of an application or efficacy supplement will not extend the initial review cycle. We may, at our discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

Under proposed § 314.60(b)(4), submission of an amendment to a supplement other than an efficacy supplement will not extend the initial review cycle. We may, at our discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

Proposed § 314.60 (b)(5) specifies that a major amendment may not include data to support an indication for a use that was not included in the original application, supplement, or resubmission.

These proposed regulations would codify for all NDAs, efficacy supplements, and resubmissions of NDAs and efficacy supplements, our current policy on extending the review period for human drug applications when a major amendment is submitted before FDA issuance of an action letter. As stated in the previous paragraphs, we believe that it is appropriate to treat amendments to unapproved efficacy supplements and amendments to resubmissions of applications and efficacy supplements, the same as amendments to unapproved NDAs. Amendments to ANDAs submitted before FDA issuance of an action letter are addressed in § 314.96, discussed in section III.D.3 of this document.

2. Procedures for Submission of a Supplement to an Approved Application (Proposed § 314.71)

The references to different types of supplemental applications in proposed §§ 314.60 and 314.110 necessitate a change to § 314.71, which addresses procedures for submission of supplements to approved applications. Current § 314.71(c) states that all procedures and actions that apply to applications under part 314, including actions by applicants and the agency, also apply to supplements. Under proposed §§ 314.60 and 314.110, a certain type of NDA supplement (i.e., efficacy supplements) will be treated the same as an NDA, while other types will be treated differently. To reflect this different treatment of certain supplements, we propose to revise § 314.71(c) to clarify that all procedures and actions that apply to applications under part 314 also apply to supplements ''except as specified otherwise in this part.''

3. Amendments to Unapproved ANDAs (Proposed § 314.96)

Our regulations on submitting amendments to unapproved abbreviated applications are set forth in § 314.96. Current § 314.96(a)(2) states that submission of an amendment containing significant data or information constitutes an agreement to extend the review period only for the time necessary to review the information and for no more than 180 days. Under § 314.96(a)(3), the submission of an amendment containing significant data or information to resolve deficiencies specified in a not approvable letter will extend the date by which we must reach a decision on the abbreviated

application only for the time necessary to review the information and for no more than 180 days.

We propose to revise § 314.96(a)(2) to substitute the term ''initial review cycle'' for ''review period.'' Our proposed revision would also clarify that an amendment to an ANDA submitted before the end of the initial review cycle that contains significant data or information could extend the initial review cycle for as many as 180 days. Thus, we are proposing to retain the Office of Generic Drugs' current approach to amendments to ANDAs.

We propose to delete § 314.96(a)(3) because the submission of an amendment to an abbreviated application following receipt of a complete response letter (i.e., a resubmission of an abbreviated application) is addressed in proposed § 314.110.

IV. Analysis of Economic Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act (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 proposed rule is not a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to prepare a Regulatory Flexibility Analysis for each rule unless the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule 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.

We believe that this proposed rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866. Because the proposed rule does not impose mandates on State, local, or tribal governments, or the private sector, that would result in an expenditure in any one year of $100,000,000 or more, we are not required to perform a cost-benefit analysis under the Unfunded Mandates Reform Act of 1995.

With respect to the Regulatory Flexibility Act, we do not believe that this proposed rule would have a significant economic impact on a substantial number of small entities. We are taking this action to amend our regulations governing applications for approval to market new drugs, generic drugs, and biological products. This action is necessary to meet a user fee performance goal to replace approvable and not approvable letters with complete response letters. The proposed rule also would revise regulations governing amendments to unapproved applications and codify terminology used in user fee performance goals affecting resubmissions of applications. As discussed in greater detail in the following paragraphs, the economic impact of these regulatory changes is not expected to be significant for any affected entity.

A. Impact of the Proposed Rule

As described in detail in sections II and III of this document, the proposed rule would do the following: (1) For NDAs and ANDAs, replace the two types of action letters currently used (approvable and not approvable letters) with complete response letters; (2) for BLAs, incorporate into the regulations an existing policy on complete response letters; (3) incorporate into regulations the terminology and procedures used in the user fee performance goals regarding NDA resubmissions; and (4) revise 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 proposed rule largely would codify current agency practices. For ANDAs, the proposed rule would revise regulations to be consistent with current practice or, where appropriate, with the provisions governing NDAs. The most significant impact of the proposed rule would be on efficacy supplements to approved NDAs and on resubmissions of applications and efficacy supplements. The impact of specific provisions of this proposed rule on NDAs, ANDAs, efficacy supplements, and resubmissions is described in greater detail in the following paragraphs.

1. Complete Response Letter

We are proposing regulatory changes that would replace approvable and not approvable letters with complete response letters. Both approvable and not approvable letters indicate that an NDA or ANDA is not approvable in its current form, and that changes are necessary or that we require additional information. A complete response letter would describe the deficiencies in an NDA or ANDA and, where appropriate, the actions necessary to place the application in condition for approval. In the past, some drug manufacturers have expressed concern that a not approvable letter sends an unintended message that a marketing application will 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 have already adopted a policy of issuing complete response letters for BLAs, and the proposed rule would simply codify 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 proposing 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 would codify agency practices regarding NDA resubmissions in place since 1998.

We are proposing to apply 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 proposed application of the Class 1 and Class 2 provisions to resubmissions of efficacy supplements would represent a regulatory change because under PDUFA II, all resubmissions of efficacy supplements would start a new 6-month review cycle. Under the proposed rule, a Class 1 resubmission of an efficacy supplement would 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 would be largely unaffected by the proposed 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 proposed rule generally would maintain current agency practice (review within 6 months) with respect to the review of other types of NDA supplements, i.e., for CMC or labeling changes (although under PDUFA III, our goal is to review within 4 months resubmissions of certain CMC supplements for which prior approval is required). For ANDA resubmissions, the proposal would codify the current practice of 6-month review.

3. Amendments to Unapproved Drug Marketing Applications

We also are proposing to revise our regulations on extending the initial review cycle following the submission of an amendment to an unapproved drug marketing application. Current regulations state, for unapproved NDAs and efficacy supplements, that submission of a major amendment extends the review cycle for the amount of time necessary to review the new information but not by more than 180 days. The proposed rule generally would extend the review cycle by 3 months if a major amendment to an application, efficacy supplement, or resubmission of an application or efficacy supplement were submitted within 3 months of the end of the initial review cycle. (The proposed rule states that we may defer review until a subsequent review cycle.) If a major amendment were submitted more than 3 months before the end of the initial review cycle, the review cycle would not be extended. These changes would codify the practice for NDAs that has been in place since 1998. However, we have 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 proposed change regarding resubmissions of efficacy supplements, we believe that it is appropriate to treat the proposed change regarding amendments to unapproved efficacy supplements as a regulatory change for purposes of this analysis.

These provisions of the proposed rule might slightly increase review times for efficacy supplements for which at least one major amendment was received during 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 might exercise our review discretion.

With respect to amendments to ANDAs, the proposed changes to regulations would codify FDA's current approach.

B. Summary of Impacts

Based on the preceding analysis, the proposed changes to provisions governing resubmissions could result in reduced review times for up to 40 percent of efficacy supplements resubmitted annually. However, the proposed provisions governing major amendments could slightly increase review times for up to 11 percent of efficacy 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 might exercise our discretion to defer review until the next cycle. ANDAs will not be significantly affected by the proposed changes to regulations.

Because this proposed rule generally amends current 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 previously noted), we certify that the proposed 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 proposed 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 proposed rule would substitute complete response letters for approvable and not approvable letters (in current §§ 314.110 and 314.120, respectively) when we take action on marketing applications. The proposed rule would retain the provisions requiring the recipient of the action letter (a complete response letter under the proposed rule) to either amend the application (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 proposed rule also would revise 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 would not change the information required in such amendments and resubmissions. OMB has approved the information collection previously discussed concerning responses to action letters under OMB control number 0910–0001, which expires on March 31, 2005.

The proposed rule would also establish regulations on the issuance of complete response letters to biologics license applicants and supplement applicants. The proposed rule would codify 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 August 31, 2005.

FDA tentatively concludes that this proposed rule contains no new collection of information. Therefore, OMB clearance under the PRA is not required.

VII. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have 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 order and, consequently, a federalism summary impact statement is not required.

VIII. Proposed Effective Date

We propose that any final rule that may issue based on this proposal become effective 30 days after the date of its publication in the **Federal Register**.

IX. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments on this proposal. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

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, it is proposed that 21 CFR parts 312, 314, 600, and 601 be 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, 371; 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 (for a drug) or § 601.3 of this chapter (for a biologic). * * *

* * * * *

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

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

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 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, 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.

Class 2 resubmission means the resubmission of an application, 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 identifying all of the deficiencies 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 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.

* * * * *

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.

* * * * *

§ 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. 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 an amendment to a supplement other than an efficacy 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.

(5) A major amendment may not include data to support an indication for a use that was not included in the original application, supplement, or resubmission.

(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.

§ 314.96 [Amended]

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)(1) Except as provided in paragraph (a)(2) 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.''

(2) For 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.

(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 review cycle may be extended 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 as follows:

a. By revising paragraph (f)(1)(ii);

b. By redesignating paragraphs (f)(2) and (f)(3) as paragraphs (f)(3) and (f)(4), respectively;

c. By adding new paragraph (f)(2); and

d. By revising the second sentence of newly redesignated paragraph (f)(3) 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 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) For 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 180-day period specified in paragraph (f)(1) of this section will be adjusted to be consistent with the agency's user fee performance goals for reviewing such applications and supplements.

(3) * * * 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 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 for which the review cycle was extended. The complete response letter will identify any amendments for which the review cycle was not extended that FDA 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) *Description of actions necessary for approval.* Where appropriate, a complete response letter will describe the actions necessary 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. For purposes of this section, a resubmission means submission by the applicant of all materials needed to fully address 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 6-month review cycle 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 (HFD–5), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. 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 under section 505(d) or (j)(4) of the act.

(c) *Failure to take action.* An applicant agrees to extend the review period under section 505(c)(1) of the act until it takes any of the actions listed in paragraph (b) of this section. For an application, FDA may consider an applicant's failure to take any of such actions within 1 year after receiving a complete response letter to be a request by the applicant to withdraw the application. For an abbreviated application, FDA may consider an applicant's failure to take any of the actions listed in paragraph (b) of this section within 6 months after receiving a complete response letter to be a request by the applicant to withdraw the abbreviated application.

§ 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 by 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 in paragraph (a)(1) by removing the phrase ''Document and Records Section, 5901–B Ammendale Rd., Beltsville, MD 20705–1266'' and by adding in its place the phrase ''Central Document Room, 12229 Wilkins Ave., Rockville, MD 20852–1833''; in paragraph (a)(3) by removing the phrase ''or § 314.120''; and by revising the introductory text of paragraph (b) to read as follows:

§ 314.440 Addresses for applications and abbreviated applications.

* * * * *

(b) Applicants must send applications and other correspondence relating to matters covered by this part for the drug products listed below to the Center for Biologics Evaluation and Research (HFM–99), Food and Drug

Administration, 1401 Rockville Pike, Rockville, MD 20852, except applicants must send a request for an opportunity for a hearing under § 314.110 on the question of whether there are grounds for denying approval of an application to the Director, Center for Biologics Evaluation and Research (HFM–1), at the same address.

* * * * *

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.

22. Section 600.3 is amended by revising paragraph (jj) to read as follows:

§ 600.3 Definitions.

* * * * *

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

* * * * *

PART 601—LICENSING

23. The authority 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).

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.

(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.* 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 receiving a complete response letter to be a request by the applicant to withdraw the application or supplement.

Dated: July 9, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 04–16476 Filed 7–19–04; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[REG–104683–00]

RIN 1545–AX88

Partial Withdrawal of Proposed Regulations Relating to the Application of Section 904 to Income Subject To Separate Limitations and Computation of Deemed-Paid Credit Under Section 902

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Partial withdrawal of notice of proposed rulemaking.

SUMMARY: This document withdraws a portion of a notice of proposed rulemaking published on January 3, 2001, relating to the application of the foreign tax credit limitation under section 904 and the deemed-paid credit under section 902.

DATES: The withdrawal of proposed §§ 1.902–0, 1.902–1 and 1.904–4(g) is made on July 20, 2004.

FOR FURTHER INFORMATION CONTACT: Bethany A. Ingwalson, (202) 622–3850 (not a toll-free number).

SUPPLEMENTARY INFORMATION:

Background

On January 3, 2001, the Treasury Department and the IRS published in the **Federal Register** (66 FR 319) a notice of proposed rulemaking (REG–104683–00) providing guidance with respect to the application of sections 902 and 904. Written comments were received and a public hearing on the proposed regulations was held on April 26, 2001. After consideration of the comments received, the Treasury Department and the IRS are withdrawing the portions of the proposed regulations that would have amended §§ 1.902–1 and 1.904–4(g). The amendments to § 1.902–1 would have terminated the pooling of a foreign corporation's post-1986 undistributed earnings and foreign income taxes if the ownership requirements of section 902(c)(3)(B) were not met as of the end of any taxable year. The amendments to § 1.904–4(g) would have disallowed look-through treatment for a dividend paid by a CFC or noncontrolled section 902 corporation out of E&P accumulated while the corporation was a look-through entity (*i.e.*, the corporation was a CFC or, for tax years beginning after December 31, 2002, a noncontrolled section 902 corporation) if paid after an intervening period during which the corporation was a non-look-through entity (*i.e.*, a less-than-10%-U.S.-owned corporation or, for tax years beginning on or before December 31, 2002, a noncontrolled section 902 corporation).

Final regulations adopting the remaining portions of the proposed regulations are being published in the Rules and Regulations section in this issue of the **Federal Register**. See the preamble to the final regulations for a discussion of the reasons §§ 1.902–1 and 1.904–4(g) are being withdrawn.

Drafting Information

The principal author of this withdrawal notice is Bethany A. Ingwalson, Office of Associate Chief Counsel (International). However, other personnel from the Treasury Department and the IRS participated in its development.

List of Subjects in 26 CFR Part 1

Income taxes, Reporting and recordkeeping requirements.

Partial Withdrawal of a Notice of Proposed Rulemaking

Accordingly, under the authority of 26 U.S.C. 7805, §§ 1.902–0, 1.902–1 and 1.904–4(g) of the notice of proposed rulemaking published in the **Federal Register** (66 FR 319) on January 3, 2001 are withdrawn.

Mark E. Matthews,

Deputy Commissioner for Services and Enforcement.

[FR Doc. 04–16375 Filed 7–19–04; 8:45 am]

BILLING CODE 4830–01–P