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Food and Drug Administration

21 CFR Parts 2, et al.

Abbreviated New Drug Regulations; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 2, 5, 10, 310, 314, 320, and 433

[Docket No. 85N-0214]

RIN 0905-AB63

Abbreviated New Drug Application Regulations

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing final regulations for most of its requirements for abbreviated new drug applications (ANDA's). FDA published a proposed rule for ANDA's in the **Federal Register** of July 10, 1989 (54 FR 28872). These regulations implement title I of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the 1984 amendments). This final rule covers subjects such as ANDA content and format, approval and nonapproval of an application, and suitability petitions. This rule does not finalize the provisions of the proposed rule on patent certification and market exclusivity; FDA is still examining the issues pertaining to those provisions and will finalize them in a future edition of the **Federal Register**.

EFFECTIVE DATE: The regulations will become effective on June 29, 1992.

FOR FURTHER INFORMATION CONTACT: Philip L. Chao, Center for Drug Evaluation and Research (HFD-362), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8049.

SUPPLEMENTARY INFORMATION:

I. Background

A. New Drug Approval: 1938 to 1962

In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act (the act). The act created a premarket approval system for drug products that required applicants seeking drug product approval to submit a new drug application (NDA) to FDA. The NDA would contain information demonstrating, among other things, that the drug product was safe. The act also provided that an NDA would automatically become effective (i.e., the product could be lawfully marketed) within a fixed period unless the agency affirmatively refused to approve the application.

In addition to drug products that had an effective NDA, many products were marketed without effective applications. These products were identical, similar, or related to products with effective NDA's. The manufacturers of these products had concluded that their drug products were generally recognized as safe, or had received advisory opinions from FDA that an NDA was not required because the products were generally recognized as safe.

In 1962, Congress amended the drug approval provisions of the act to require affirmative approval to NDA's before marketing. The amendments required applicants to show that their products were both safe and effective (Pub. L. 87-781 (October 10, 1962)). Thus, on or after October 10, 1962, a person could not market a new drug without an approved NDA that contained sufficient safety information as well as substantial evidence establishing the drug's effectiveness for its intended uses.

The 1962 amendments also deemed NDA's that had become effective before October 10, 1962, to be approved. As with postenactment drugs, the 1962 amendments required these "pre-1962" drugs to be shown to be effective for their intended uses. Consequently, FDA began a program to evaluate the drugs that had been deemed approved to determine whether there was substantial evidence of their effectiveness. This systematic evaluation and the implementation of FDA's findings became known as the Drug Efficacy Study Implementation (DESI). Under DESI, FDA contracted with the National Academy of Sciences/National Research Council (NAS/NRC), which established expert panels to review available evidence of effectiveness and to provide recommendations to FDA. FDA considered the NAS/NRC panels' recommendations about the effectiveness of these DESI drugs, and announced its conclusions through **Federal Register** notices. These notices, known as DESI notices, contain the acceptable marketing conditions for the class of drug products covered by the notice.

B. The ANDA Procedure for Pre-1962 Drugs

If a manufacturer had a pre-1962 NDA in effect for a drug product, FDA continued its approval if the manufacturer submitted a supplemental new drug application to conform the product's indications for use to those determined to be effective in the DESI review. Yet, as stated above, many drug products had active ingredients and indications that were identical or very similar to the drug products found to be effective in the DESI review but lacked NDA's themselves. In implementing the DESI program with respect to these duplicate products, FDA concluded that each such drug product was a "new drug" that required its own approved NDA before it could be legally marketed (*United States* v. *Generix Drug Corp.*, 460 U.S. 453 (1983)). Additionally, FDA issued a policy statement in the **Federal Register** of May 28, 1968 (33 FR 7758) that revoked the earlier advisory opinions that drugs could be marketed without prior FDA clearance. This rule was codified at 21 CFR 310.100.

Shortly thereafter, FDA created the ANDA procedure for the approval of duplicate products in reliance on the DESI evaluation. In brief, after the DESI program had found a particular drug product to be effective and suitable for ANDA's, FDA published a **Federal Register** notice announcing its conclusions. Any manufacturer of a duplicate drug product that did not have an approved NDA was then required to submit an ANDA to obtain approval to market the duplicate version of the approved drug. (See 34 FR 2673, February 27, 1969; 35 FR 6574, April 24, 1970; and 35 FR 11273, July 14, 1970.)

Before 1984, FDA based these ANDA approvals on the theory that the evidence of effectiveness necessary for approval of an NDA had been provided, reviewed, and accepted during the DESI process. Evidence of the drug's safety had been determined on the basis of information contained in the pioneer NDA and by the subsequent marketing experience with the drug. FDA required ANDA applicants to submit information that showed the applicant's ability to manufacture a product of acceptable quality whose safety and effectiveness were equivalent to the drug product whose safety and effectiveness had been established. Thus, ANDA applicants provided information on the drug product's formulation, manufacture, quality control procedures, and labeling. DESI notices specified additional information, such as bioavailability/bioequivalence data, for the ANDA.

C. Procedures for Duplicates of Post-1962 Drugs ("Paper NDA" Policy)

FDA never extended its ANDA policy for pre-1962 drugs to duplicates of drugs first approved for marketing on or after October 10, 1962, although it did consider the possibility of such an extension either by regulation or through legislation. (See 54 FR 28872 at 28873 and citations therein.) As patents began to expire for many post-1962 drugs, including some high volume, therapeutically important drug products,

many manufacturers became interested in changing the NDA system to permit ANDA's for post-1962 drug products.

FDA did allow some duplicate drug products of drugs first approved after 1962 to be marketed under its "paper NDA" policy. (See 46 FR 27396, May 19, 1981.) This policy permitted FDA to approve NDA's for post-1962 drug products on the basis of safety and effectiveness information derived primarily from published reports based on well-controlled studies. This meant that manufacturers did not have to conduct their own tests, but adequate literature, including detailed reports of adequate and well-controlled studies, was available for only a fraction of the post-1962 drugs. Moreover, the staff effort involved in reviewing paper NDA's ultimately proved to be a substantial and inefficient use of agency resources.

D. The Drug Price Competition and Patent Term Restoration Act of 1984

From 1978 to 1984, Congress considered various bills that would have authorized an ANDA procedure for duplicate versions of post-1962 drug products. Other bills under consideration during this period sought to restore patent life lost while awaiting Federal marketing approval. Congress combined the ANDA procedure for post-1962 drug products and patent term restoration in the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417).

The law consisted of two different titles. Title I authorized the approval of duplicate versions of drug products, approved under section 505 of the act, under an ANDA procedure. Title II authorized the extension of patent terms for approved new drug products (including antibiotics and biological drug products), some medical devices, food additives, and color additives. Congress intended the two titles to provide a careful balance between promoting competition among brand-name and duplicate or "generic" drugs and encouraging research and innovation.

Title I amended section 505 of the act by establishing a statutory ANDA procedure for duplicate and related versions of human drugs approved under section 505(b) of the act. These procedures are inapplicable to antibiotics (which are approved under section 507 of the act) and biological drug products licensed under 42 U.S.C. 262. The statute adopted, with few modifications, the agency's ANDA procedure for pre-1962 drugs. It required all applicants to provide certain patent information; provided for the submission and approval of applications for which the investigations relied on by the applicant to satisfy the "full reports" of safety and effectiveness requirement were not conducted by or for which the applicant had not obtained a right of reference or use from the person who conducted the investigations; established rules for disclosure of safety and effectiveness data submitted as part of an NDA; and provided specific time periods during which ANDA's and NDA's for certain drug products may not be submitted or approved. The act also required FDA to promulgate new regulations implementing the statute. In the **Federal Register** of July 10, 1989 (54 FR 28872), FDA published a proposed rule on ANDA's. This final rule contains must of the provisions contained in that proposal.

FDA published a final rule implementing Title II in the **Federal Register** of March 7, 1988 (53 FR 7298). This rule is codified at 21 CFR Part 60.

II. Highlights of this Final Rule

This final rule amends 21 CFR Part 314 to establish new requirements and procedures for NDA and ANDA applicants under the 1984 amendments. The rule also revises the bioavailability and bioequivalence requirements at 21 CFR part 320 to conform to the 1984 amendments and current agency policy. Minor conforming amendments are made to 21 CFR parts 2, 5, 10, 310, 314, and 433. Additionally, because the agency will issue final regulations governing patent certification and marketing exclusivity requirements at a future date, FDA has revised or deleted cross-references to those provisions and, where possible, replaced them with statutory citations.

The final rule's major provisions are as follows:

A. Abbreviated Applications

The statutory provisions governing ANDA requirements and procedures are at section 505(j) of the act (21 U.S.C. 355(j)).

The statute permits ANDA's for: (1) A drug product that is the "same" as a drug product listed in the approved drug product list published by FDA (the "listed drug") with respect to active ingredient(s), route of administration, dosage form, strength, and conditions of use recommended in the labeling; and (2) a drug product with certain changes from a listed drug if FDA has approved a petition from a prospective applicant permitting the submission of an ANDA for the changed drug product.

Subpart C of part 314 addresses an ANDA applicant's requirements and responsibilities. The final rule is substantially similar to the proposal, although FDA has made some minor changes, such as requiring applicants to include a table of contents in the review copies of an ANDA (21 CFR 314.94(a)(2)), and other minor changes regarding periodic reports from ANDA holders (21 CFR 314.98). One noteworthy change concerns the chemistry, manufacturing, and controls section of an ANDA. Under the proposed rule, applicants would have been required to identify and characterize inactive ingredient differences between their products and those in the reference listed drug. FDA received numerous comments stating that, for many drug products, applicants would be unable to discover which inactive ingredients were used in the reference listed drug. Consequently, the final rule requires applicants to identify and describe such differences regarding inactive ingredients only for topical drug products, drug products intended for parenteral use, and drug products intended for ophthalmic or otic use. The inactive ingredients for these products are listed on the products' labels. For other drug products, the final rule requires applicants to identify and characterize only the inactive ingredients in their own products.

FDA has also revised some policies that were announced in the preamble to the proposed rule. For example, the preamble to the proposed rule indicated that FDA would accept an ANDA submission that contained a bioequivalence protocol. This policy had the unintended effect of encouraging applicants to file incomplete ANDA's. Therefore, FDA is announcing that it will no longer accept an ANDA that does not contain the results of a complete bioequivalence study if such a study is required for approval. These and other changes are described in more detail in the responses to comments below.

B. ANDA Suitability Petitions

Under section 505(j)(2)(C) of the act, an ANDA applicant may petition FDA for permission to file an ANDA for a drug product that has one different active ingredient in a combination product, or whose route of administration, dosage form, or strength differs from that of the listed drug. These are the only types of changes permitted in an ANDA.

The final rule, at 21 CFR 314.93, describes the information that a petitioner must include in its petition. The information must demonstrate that the change from the listed drug requested for the proposed drug product

may be adequately evaluated for approval without data from investigations to show the proposed drug product's safety or effectiveness and that a drug product with a different active ingredient may be adequately evaluated for approval as safe and effective on the basis of information required to be submitted in an ANDA.

In the preamble to the 1989 proposed rule, FDA invited comments on a policy that would provide for the confidentiality of any petition submitted under section 505(j)(2)(C) of the act until FDA either approved or disapproved the petition. At the time of the proposed rule, FDA's policy was to make these petitions available to the public. The agency received an equal number of comments in favor of and opposed to such a policy. The comments favoring confidentiality argued that the public availability of suitability petitions would adversely affect the petitioner's commercial interests. The comments opposing confidentiality said that the public availability of these petitions would enhance the decisionmaking process. FDA agrees with the latter view. By making suitability petitions publicly available, FDA has received valuable comments and information from third parties. These comments and information have contributed to the agency's evaluation of some suitability petitions. Consequently, FDA will continue its policy of making such petitions available to the public.

An ANDA submitted under an approved petition would generally be required to contain the same information as an ANDA for a drug product that is the same as a listed drug except that FDA may require additional information regarding the difference between the proposed drug product and the listed drug. Additionally, FDA requires that the listed drug referred to in the ANDA be the one upon which the petition was based and that the applicant refer to the petition in its ANDA and include a copy of FDA's response approving submission of an ANDA.

C. 505(b)(2) Applications

The 1984 amendments also amended section 505(b) of the act (21 U.S.C. 355(b)) to create another type of application. These applications, known as 505(b)(2) applications, are similar to applications under the agency's "paper NDA" policy. Unlike the paper NDA policy, however, section 505(b)(2) of the act applies to applications that contain investigations relied upon by the applicant to provide full reports of safety and effectiveness where the investigations were not conducted by or for the applicant and the applicant has not obtained a right of reference or use from the person who conducted the investigations. (See 21 U.S.C. 355(j)(2).) Thus, section 505(b)(2) of the act is not restricted to literature-supported NDA's for duplicates of approved drugs; it covers all NDA's for drug products that rely on studies not conducted by or for the applicant or for which the applicant does not have a right of reference.

A 505(b)(2) application is submitted under section 505(b)(1) of the act. Consequently, these applications are subject to the same statutory provisions as full NDA's. The statute, however, gives 505(b)(2) applicants additional obligations, such as patent certification, that are similar to those of ANDA applicants. The final rule addresses 505(b)(2) application procedures at 21 CFR 314.50.

The preamble to the proposed rule (54 FR 28872 at 28891) asked whether FDA should adopt a policy whereby a 505(b)(2) application for a drug product with a change in dosage form, strength, route of administration, or active ingredient would be treated as a petition under section 505(j)(2)(C) of the act. Most comments opposed such a policy, asserting that the policies and procedures for 505(b)(2) applications are or should be distinct from those for suitability petitions. After careful consideration, the agency believes that the policy would prolong review of 505(b)(2) applications and suitability petitions. Consequently, FDA will not adopt the proposed policy.

D. Withdrawal or Suspension of Approval of an ANDA

The statute authorizes the Secretary of Health and Human Services (the Secretary) to withdraw or suspend the approval of any ANDA for a generic drug if: (1) Grounds exist for withdrawal under section 505(e) of the act; (2) the approval of the listed drug referred to by the generic applicant is withdrawn or suspended; or (3) the manufacturer voluntarily withdraws the listed drug from sale for what the agency determines are safety or effectiveness reasons. The final rule contains provisions on withdrawal and suspension at 21 CFR 314.150 to 314.153.

III. Comments on the Proposed Rule

Section 10.30—Citizen Petition

Proposed § 10.30 (e)(2) and (e)(4) would have amended FDA's citizen petition regulations to provide for responses to petitions filed in accordance with section 505(j)(2)(C) of the act.

1. FDA received one comment on proposed § 10.30(e)(2). The comment agreed with the provision, and FDA has finalized it without change.

Section 10.45—Court Review of Final Administrative Action; Exhaustion of Administrative Remedies

2. Two comments objected to proposed § 10.45(d), which would make FDA's response to a petition for reconsideration, rather than a response to a petition under section 505(j)(2)(C) of the act, final agency action. Both comments said that FDA had no authority to require a petition for reconsideration and would give petitioners the right to request a hearing or declare FDA's response to the suitability petition to be final agency action.

FDA disagrees with the comments. FDA has the authority to require adherence to a petition for reconsideration procedure, and such a requirement is practical in this case. From a practical standpoint, the agency receives a large number of suitability petitions each year. If every response to a suitability petition were to be considered as final agency action, the agency would be obliged to devote more resources to each petition to create a comprehensive administrative record. This approach would prolong the review of all suitability petitions without any appreciable benefit to petitioners or the agency. In fact, requiring a petition for reconsideration is to the petitioner's benefit because it ensures that senior FDA officials review the decision on the suitability petition. As for the authority to require a petition for reconsideration, the agency does not agree that it lacks authority to establish by regulation what constitutes final agency action on a petition.

Section 310.305—Records and Reports Concerning Adverse Drug Experiences on Marketed Prescription Drugs for Human Use Without Approved New Drug Applications

3. FDA received one comment on proposed § 310.305 (a)(3) and (c)(4), which, in part, would require persons to report or review reports of therapeutic failure. The proposed rule would amend the existing regulation, which required manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved NDA or ANDA to maintain records and report to FDA "(1) all serious, unexpected adverse drug experiences associated with the use of their drug products and (2) any significant increase in the frequency of a serious, expected

adverse drug experience." The comment suggested that FDA delete "therapeutic failure" and replace it with "significant failure of expected pharmacological action."

The agency declines to adopt the comment's suggestion. Section 310.305 uses the term "therapeutic failure" to correspond to similar language for adverse drug experience reporting for drugs subject to premarket approval. (See § 314.80; 54 FR 28872 at 28911.) In the preamble to the proposed rule, FDA explained that it was deleting the word "significant" from the phrase "any significant failure of expected pharmacological action" because the word "significant" had been a source of confusion and ambiguity. (See 54 FR 28872 at 28889.) Thus, FDA proposed to amend §§ 314.80 and 310.305 to require reports of "therapeutic failure" to eliminate this confusion and require all reports of therapeutic failure (54 FR 28872 at 28889).

Section 314.1—Scope

4. FDA received no comments on the proposed changes to 21 CFR 314.1, but did receive two general comments regarding the proposed rule's scope. One comment asked FDA to permit ANDA's for duplicates of "drug substances for which the specifications are very tightly drawn for both potency and purity," such as insulin preparations, and for copies of biotechnology-derived drug products. The second comment recommended that FDA accept ANDA's with warnings or precautions in addition to those on the reference listed drug's label, provided that such information was not indicative of diminished safety or effectiveness of the generic drug product.

Section 505(j) of the act permits ANDA's only for duplicate and related versions of previously approved drug products. The ANDA applicant relies on a prior agency finding of safety and effectiveness based on the evidence presented in a previously approved new drug application. If investigations on a drug's safety or effectiveness are necessary for approval, an ANDA is not permitted. Thus, under the statute, an ANDA would only be permitted for a drug product with "tight specifications" or a biotechnology-derived drug product only if such a product is the same as a product previously approved under section 505 of the act or if FDA has approved submission of an ANDA under a petition filed under section 505(j)(2)(C) of the act.

As for accepting ANDA's with additional warnings or precautions, section 505 (j)(2)(A)(v) and (j)(3)(G) of the act requires that the applicant's proposed labeling be the same as that of the reference listed drug unless: (1) The labeling differences are due to an approved petition under section 505(j)(2)(C) of the act (otherwise referred to as a "suitability petition"); or (2) the drug product and the reference listed drug are produced or distributed by different manufacturers. (See 21 U.S.C. 355 (j)(2)(A)(v) and (j)(3)(G).) Thus, the exceptions in section 505 (j)(2)(A)(v) and (j)(3)(G) of the act are limited. In addition, under the patent and exclusivity provisions of the act, the ANDA labeling may be required to carry fewer indications than the reference listed product's labeling or to have other labeling differences. In the preamble to the proposed rule, the agency described various types of labeling differences that might fall within the permitted exceptions. An ANDA applicant is required to include in its ANDA a side-by-side comparison of the applicant's proposed labeling with the currently approved labeling for the reference listed drug. The agency will carefully review all differences annotated by the applicant in determining if such differences fall within the limited exceptions permitted by the act.

Section 314.3—Definitions

FDA received 14 comments concerning the definitions of "listed drug" and "reference listed drug" under proposed § 314.3. The proposed rule had defined a "listed drug," in part, as:

> • • • a new drug product that has been approved for safety and effectiveness under section 505(c) or approved under section 505(j) of the act, the approval of which has been withdrawn or suspended under section 505(e) (1) through (5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's inclusion in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) or any current supplement to the list.

The proposed rule defined a "reference listed drug" as "the listed drug identified in an abbreviated new drug application or identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application."

5. With respect to the "listed drug" definition, one comment objected to the exclusion of drugs marketed in compliance with an over-the-counter (OTC) monograph and products with OTC and prescription indications. A second comment said that FDA must list DESI products and post-1962 approved drug products even if the drug products were no longer marketed by September 24, 1984, because section 505(j)(6)(A)(i) of the act requires those products be listed. Four comments objected to listing drugs that have delayed effective dates of approval, while one comment favored listing such drugs.

FDA agrees in part and disagrees in part with the comments. As defined in section 505(j)(6) of the act, a listed drug is one that was approved for safety and effectiveness under section 505(c) of the act or approved under section 505(j) of the act. Drug products marketed in compliance with an OTC monograph rather than pursuant to an approval under section 505(c) or (j) of the act are not listed drugs under the statute.

With respect to DESI products and post-1962 approved drug products that are no longer marketed, FDA stated its position in the preamble to the proposed rule. In brief, FDA declines to allocate its scarce resources to publish and maintain lists of drug products that no longer generate interest with respect to marketing (54 FR 28877 through 28878). FDA does, however, maintain a list of discontinued products as an appendix to the list, and has created a procedure to return these products and other discontinued products to the list where appropriate. If a drug firm wishes to submit an ANDA for a generic version of one of these drug products, it may petition FDA to relist the drug product and provide information to show that the drug product was not withdrawn from sale due to safety or effectiveness reasons.

With respect to drug products with delayed effective dates of approval, FDA has determined that such products should not be listed. An approval with a delayed effective date is tentative and does not become final until the effective date. FDA has concluded that only drug products with final, effective approvals are to be listed under section 505(j)(6) of the act. FDA has amended the definitions of "listed drug" and "the list" to clarify that only drugs with an effective approval are listed drugs.

Similarly, with respect to drug products that are subject to the DESI program and do not meet the conditions for approval of effectiveness as set forth in a DESI notice, FDA has reexamined its policy and no longer regards the DESI notice published in the **Federal Register** as a "listed drug." Section 505(j)(6) of the act describes a "listed drug" as a drug that has been approved for safety and effectiveness. A drug product that must satisfy the conditions for approval of effectiveness as set forth in a DESI notice, therefore, does not fall within section 505(j)(6) of the act and cannot be a listed drug. Therefore, the

agency has revised the definition of listed drug so that a DESI notice will not suffice as a "listed drug."

6. Five comments addressed the definition of "reference listed drug." Three comments suggested that the oldest or first NDA product be the reference listed drug while one comment suggested that any FDA-approved drug be a "referenced listed drug." Another comment recommended designating "reference listed drugs" in the publication titled, "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the "Orange Book."

As noted in the preamble to the proposed rule, FDA intends the reference listed drug to be the same drug product selected by the agency as the reference standard for bioequivalence determinations. Therefore, FDA has revised the definition of "reference listed drug" to make clear that a "reference listed drug" is a listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application. In some instances, such as the submission of an ANDA for a product with multiple strengths, there may be more than one reference listed drug. In these instances, FDA considers each strength to represent a different drug product and will require an ANDA applicant to demonstrate that each proposed drug product is bioequivalent to its corresponding reference listed drug. FDA will identify in future editions of the Orange Book those approved drugs that FDA regards as reference listed drugs. In the interim, FDA will maintain a list of reference listed drugs at the Dockets Management Branch (HFA-305), Food and Drug Administration, room 1–23, 12420 Parklawn Dr., Rockville, MD 20857, until the Orange Book can be revised. FDA hopes that designating a single reference listed drug against which all generic versions must be shown to be bioequivalent will avoid possible significant variations among generic drugs and their brand name counterparts. Such variation could result if generic drugs established bioequivalence to different reference listed drugs.

7. One comment recommended defining "appropriate reliance" for purposes of section 505(b)(2) applications. The comment noted that the preamble to the proposed rule had stated "Appropriate reliance on an analysis of (spontaneous) adverse reaction reports will not cause application to be one described by section 505(b)(2) or 505(c)(3)(D)(of the act." (54 FR 28872 at 28891). The comment said it did not believe that an application containing an analysis of adverse reaction reports in place of safety studies "should be considered a full application for the purpose of 'breaking exclusivity' granted to another sponsor's drug."

FDA believes that the comment has misinterpreted the agency's position. The preamble to the proposed rule stated that, for drug products with a U.S. marketing history, an analysis of the spontaneous adverse reaction reports "may, in some cases, be substituted for some of the safety data" in a full NDA (54 FR 28872 at 28891). The agency believes that an analysis of spontaneous adverse reaction can provide some safety information when: (1) The drug product has a U.S. marketing history; and (2) there is a substantial amount of adverse drug reaction experience for that drug product. For example, an applicant could submit such an analysis to substitute for certain animal studies that would otherwise be required to show the kinds of risks that might be expected when the drug is tested in humans, or to show which certain, infrequent side effects occur rather than conduct large, Phase 3 clinical studies to prove the same result. Thus, FDA does not contemplate that an applicant under section 505(b)(1) of the act will substitute an analysis of adverse reaction reports for all safety information.

Section 314.50—Content and Format of an Application

The proposed rule contained several revisions and additions to the existing requirements at 21 CFR 314.50. The proposed revisions were minor. For example, under proposed § 314.50(a)(2), an applicant would be required to provide a statement whether the submission is an original application, a 505(b)(2) application, a resubmission, or a supplement to an application. The proposed additions focused on patent information and certifications and claimed exclusivity, and are not included in this final rule.

8. Proposed § 314.50(g)(3) would require an applicant who is submitting an application under section 505(b) of the act and who has a "right of reference or use" as defined in § 314.4(b) to include a "written statement signed by the owner of the data from each such investigation that the applicant may rely on in support of the approval of its application, and provide FDA access to, the underlying raw data that provide the basis for the report of the investigation submitted in its application." One comment would provide FDA access to the underlying raw data "only if FDA would not otherwise have access to the information that is needed for an adequate review of the application."

Section 314.50(g)(3) simplifies the process in which FDA can have access to raw data if such data are needed to review an application. Without this provision, if FDA determined that it needed to examine the raw data, it would be obligated to suspend the review process, request that the applicant obtain a written statement from the owner of the data to give FDA access to the data, and wait for the written statement to arrive before continuing its review. The provision, therefore, streamlines the review process by eliminating the need for requests and correspondence between FDA, applicants, and owners of data referenced by applicants after FDA had begun its review. The agency will utilize this authority when it believes that access to the raw data is necessary for reviewing the application.

Section 314.54—Procedure for Submission of an Application Requiring Investigations for Approval of a New Indication for, or Other Change from, a Listed Drug

FDA received two comments on proposed § 314.54. This provision would permit any person seeking approval of a drug product that represents a modification of a listed drug and for which investigations other than bioequivalence or bioavailability studies are essential to the approval of the change to submit a 505(b)(2) application.

9. One comment said FDA should revise proposed § 314.54(a) to state that a 505(b)(2) application is appropriate for changing a drug from prescription to OTC status.

FDA declines to adopt the comment. The regulation, as written, does not preclude submission of a 505(b)(2) application to change a drug from prescription to OTC status, so the suggested revision is unnecessary.

10. A second comment objected to proposed § 314.54(b) because it would prevent applicants from submitting applications requiring investigations for approval of a change from a listed drug for drugs whose only difference from the reference listed drug is that the extent to which the listed ingredients are absorbed or otherwise made available to the site of action to a lesser degree compared to the reference listed drug. The comment said FDA should judge drug products individually.

FDA declines to accept the comment. Differences in the extent to which a drug is absorbed will affect the drug's

therapeutic effectiveness. For example, a drug whose extent of absorption is less than that of the reference listed drug may be less effective or even ineffective. Consequently, FDA will not accept applications for products under § 314.54(b) whose extent of absorption is less than that for the reference listed drug.

FDA has, however, amended § 314.54(b) to state that it also will not accept an application under § 314.54 for a product whose only difference from the reference listed drug is an unintentional, lesser rate of absorption. FDA is making this change because a drug whose rate of absorption is unintentionally less than that of the reference listed drug may be less effective.

Section 314.55—Abbreviated Application; Section 314.56—Drug Products for Which Abbreviated Applications are Suitable

FDA received no comments on its proposal to remove these provisions, and, therefore, has removed them from 21 CFR part 314.

Section 314.60—Amendments to an Unapproved Application

11. FDA received two comments on proposed § 314.60. In general, proposed § 314.60 stated when an applicant could submit an amendment to an application filed under § 314.100 but not yet approved, and also stated when an unapproved application could not be amended. One comment asked FDA to explain how exclusivity would be affected if a section 505(b)(2) application is amended before another section 505(b)(2) application, which had been filed earlier, is approved. The second comment claimed that § 314.60(d) would permit section 505(b)(2) applications to become effective regardless of new drug exclusivity. This comment said FDA should revise the rule to declare that a section 505(b)(2) application "that would not be approvable but for a previously approved application * * * be made subject to the exclusivity of that previously approved application."

The preamble to the proposed rule explained that, for concurrently pending 505(b)(2) applications, any 505(b)(2) application submitted to FDA before the approval of another NDA that qualifies for exclusivity under section 505(c)(3)(D)(ii) of the act (granting 5 years of exclusivity) is "not affected by this exclusivity provision." (54 FR 28872 at 28901.) This is because section 505(c)(3)(D)(ii) of the act prohibits only the "submission," and not the approval, of a 505(b)(2) application that refers to a previously approved application. The only exception to the policy on concurrently pending 505(b)(2) applications is where "the first applicant to obtain approval and to qualify for exclusivity publishes its data and the competing applicant amends its application to include the first applicant's published data * * *. Where that data would be essential to the approval of the competing application, the second application will be deemed to refer to the first application" and not permitted to avoid exclusivity. Id. This policy is covered under § 314.60(b)(1)(ii), so the comment's suggestion is unnecessary.

FDA disagrees with the second comment's assertion that the rule permits section 505(b)(2) applications to become effective regardless of exclusivity. The statute clearly states that the Secretary may not approve, or, in one case, that applicants cannot submit, an application before an exclusivity period expires. (See 21 U.S.C. 355(c)(3)(D)(i) through (c)(3)(D)(v).) The rule observes these restrictions and pertains only to amendments to unapproved applications; it does not address approvals. Section 314.60(b) is, in fact, designed to protect an applicant's exclusivity under section 505(c)(3)(D)(ii) of the act while simultaneously preserving an applicant's incentive to publish the studies on which approval was based. Thus, FDA does not adopt the comment's suggested language.

Section 314.70—Supplements and Other Changes to an Approved Application

FDA received no comments on this provision, but has amended the provision to adopt references to statutory, rather than regulatory, provisions or to explain what information should be provided. However, the agency wishes to remind ANDA applicants that, as noted in paragraph 4 above, the labeling for an ANDA product must, with few exceptions, correspond to that for the reference listed drug.

Section 314.71—Procedures for Submission of a Supplement to an Approved Application

FDA received no comments on this provision and has finalized it without change.

Section 314.80—Postmarketing Reporting of Adverse Drug Experiences

FDA proposed several changes to 21 CFR 314.80 under the proposed rule. Section 314.80(a) under the existing regulation defined an "adverse drug experience," in part, as "any significant failure of expected pharmacological action." The proposed rule would delete the adjective "significant" from this definition and, as a result, require reporting of "any failure of expected pharmacological action." The proposed rule also would require applicants to review all adverse drug experience information "obtained or otherwise received by the application from any source, foreign or domestic," and to review periodically the frequency of reports of adverse drug experiences "that are both serious and expected and reports of therapeutic failure (lack of effect), regardless of source, and report any significant increase in frequency as soon as possible * * *."

12. FDA received several comments on adverse drug experience reporting under proposed § 314.80. Four comments supported the rule. Five objected to deleting the adjective "significant" from the phrase "any significant failure of expected pharmacological action" in the existing definition of "adverse drug experience," or asked FDA to limit the rule. The comments said the rule would require additional reports and generate reports with little value.

As stated in the preamble to the proposed rule, FDA deleted the word "significant" from § 314.80 because the word has been a source of confusion and ambiguity (54 FR 28872 at 28889). By amending the rule, FDA intended to require reports of any drug failure, as the agency considers all such failures to be significant. Id. This modification will provide a complete picture of adverse drug experiences, rather than selected reports, and will improve the agency's ability to determine whether it should take regulatory action.

13. One comment said a "therapeutic failure" should include excessive or exaggerated responses to a drug.

FDA declines to amend the rule as suggested. FDA does not consider such responses to be "therapeutic failures" under § 314.80. They are, however, covered under § 314.80 because they usually manifest themselves as adverse drug experiences. Consequently, applicants are obligated to report them as adverse drug experiences.

Section 314.81—Other Postmarketing Reports

The proposed rule would amend 21 CFR 314.81 to require applicants to submit a Form FDA 2657 (Drug Product Listing) within 15 working days of the withdrawal from sale of a drug product. The proposed rule also contained details regarding the information to be submitted, such as the National Drug Code number, the drug product's

established name and proprietary name, and the date of withdrawal from sale.

14. One comment asked FDA to clarify whether an applicant's obligation to submit postmarketing reports begins when FDA approves its ANDA or when the ANDA approval becomes effective.

Although the preamble to the proposed rule said proposed § 314.81 would apply upon ANDA approval regardless of the ANDA's effective date (54 FR 28872 at 28889), FDA has reconsidered this position in light of its policy on delayed effective dates and approvals. FDA does not consider a drug to be approved until the effective date of approval and regards those drug products with delayed effective dates as having tentative approvals. This policy affects § 314.81 because section 505(k) of the act authorizes reporting requirements for drug products that have an approval "in effect." Thus, an applicant's obligation to submit postmarketing reports will begin when the ANDA approval becomes effective.

15. Two comments addressed the 15-day reporting deadline in proposed § 314.81(b)(3)(iii)(*a*). One comment said a company "does not always know within 15 days of its last shipment that it intends to discontinue marketing a product" and "it is not always clear to a company whether a product is going to be withdrawn from marketing or just temporarily suspended." The comment would have applicants notify FDA that they will withdraw a product when they decide to permanently withdraw the product from sale. The second comment added that the existing rule's annual reporting requirement was satisfactory.

FDA believes the first comment misinterprets the provision. FDA does not expect parties to submit reports within 15 days from the date of their last shipment. The 15-day period begins from the time the firm decides to withdraw the product from the market. Such withdrawals are not limited to permanent withdrawals; FDA is interested in any decision to discontinue marketing because of the possible implications for the product's safety and efficacy. The agency also declines to replace the 15-day reporting period with an annual reporting requirement as suggested by the second comment. The withdrawal of an approved NDA drug product may affect the marketing of duplicate ANDA drug products, so timely reports of drug product withdrawals may be very important.

Section 314.92—Drug Products for Which Abbreviated Applications May be Submitted

FDA received four comments on proposed § 314.92. The proposed rule stated that abbreviated applications are suitable for certain drug products, such as drug products that are the same as a listed drug, drug products that meet the monograph for an antibiotic drug for which FDA has approved an application, drug products for which FDA has found an ANDA to be suitable and has announced such a finding in the Federal Register, and drug products that FDA has declared to be suitable for an ANDA submission under the petition procedures.

16. One comment asked FDA to refuse ANDA's for DESI drugs on the grounds that the statute only applies to post-1984 ANDA's. The comment noted that DESI drugs are reviewed by category rather than active ingredient and said some DESI active ingredient categories lack a "readily identifiable pioneer NDA product." Another comment supported ANDA's for DESI drugs.

The ANDA provisions of the 1984 amendments are applicable to all generic drugs for which approval is sought after September 24, 1984, the date on which the statute was enacted. Perpetuating different ANDA systems for pre-1962 drugs and post-1962 drugs would be needlessly confusing, illogical, and inefficient to FDA, the public, and industry. Therefore, FDA has included DESI drugs in these regulations.

Upon further consideration, FDA agrees that ANDA's may be inappropriate for some DESI drug products. In the DESI process, a DESI-reviewed NDA or ANDA is usually considered approved for safety and effectiveness through the approval of a supplement that brings the NDA or ANDA drug product into compliance with a DESI-upgrade notice. The DESI-upgrade notice describes what information the NDA or ANDA holder must provide in order for its drug product to be considered effective. If the NDA or ANDA holder complies with the notice through an approved supplement, then the drug product is considered to be safe and effective and can be listed in the Orange Book. Once this occurs, a person may be able to submit an ANDA for the product. However, if the NDA or ANDA holder fails to comply with the notice, the NDA or ANDA drug product is not considered to be approved for effectiveness and cannot be a listed drug. Under these circumstances, an ANDA cannot be submitted because there is no "listed drug." Therefore, FDA has revised § 314.92 by removing paragraph (a)(3) and renumbering paragraph (a)(4) as (a)(3). An applicant seeking to rely on the findings reflected in a DESI-upgrade notice, in the absence of a listed drug, should submit its application under section 505(b)(2) of the act.

Once a drug subject to a DESI notice is approved for safety and effectiveness and can serve as a listed drug, the agency will require the submission of an ANDA under section 505(j) of the act for a generic version of the product. As a matter of policy, the agency does not accept applications under section 505(b)(2) of the act when there is a listed drug that would provide a basis for an application under section 505(j) of the act. For clarity, FDA has added a new paragraph (d)(9) in § 314.101. The issue had been discussed in the preamble to the proposed rule (54 FR 28890 through 28891). At that time, the agency proposed to treat a 505(b)(2) application as submitted under section 505(j) of the act if the application was for a duplicate of a listed drug eligible for approval under section 505(j) of the act. Id. FDA believes that the policy it is describing in new § 314.101(d)(9), that an application for a drug such as this needs to be submitted by the applicant as an ANDA under section 505(j) of the act, is the preferable approach.

17. Two comments concerned proposed § 314.92(a)(1), which said, in part, that an ANDA would be suitable for a drug product that is the same as a listed drug and that the term "same as" means "identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except that conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted." The proposed rule would also require potential applicants to comply with § 314.122, "Submitting an abbreviated application for, or a 505(j)(2)(C) petition that relies on, a listed drug that is no longer marketed," if the listed drug had been voluntarily withdrawn or not offered for sale by its manufacturer. One comment asked FDA to define "strength." The second objected to the language on voluntary withdrawals. The comment said NDA holders should disclose the reasons for withdrawing a product, and FDA should determine whether those reasons raise safety or efficacy questions, and then give ANDA holders an opportunity to examine and respond to the information on the withdrawal.

"Strength" refers to the amount of the product's active ingredient and is usually expressed in terms of weight. For example, a drug that is available as a 50 milligram (mg) tablet and a 100 mg tablet has two "strengths."

As for voluntary withdrawals and the reasons for a withdrawal, FDA refers

the reader to its discussion of identical comments at § 314.161 below.

17a. Additionally, although the preamble to the proposed regulation stated: "Section 507(a) of the act permits the submission of abbreviated applications for *duplicates* of all antibiotics the agency has already approved for marketing" (emphasis added) (54 FR 28872 at 28878), the proposed regulation (§ 314.92(a)(2)) referred only to products that meet the monograph. Because, in some instances, a generic antibiotic may be a duplicate of an approved antibiotic but may not meet the monograph in every respect for that approved antibiotic, the agency has broadened the language of the proposed regulation to include generic antibiotics that either are duplicates of, or meet the monograph for, the approved antibiotic. This change is made at the agency's initiative to reflect the intent of the agency expressed in the preamble to the proposed regulation.

Section 314.93—Petition To Request a Change from a Listed Drug

Proposed § 314.93(b) stated that a person who wants to submit an ANDA for a drug product "which is not identical to a listed drug product in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one of the active ingredients in a listed combination drug, must first obtain permission from FDA to submit such an abbreviated application."

18. Most comments agreed with the proposal, but one comment suggested that the rule be revised to state that FDA will not accept a suitability petition if the proposed drug product has different inactive ingredients which "may have some effect on the safety or efficacy of the altered product." Another comment asserted that the safety and effectiveness of a proposed new combination drug cannot be determined without drug interaction data.

FDA declines to accept the comments. Under the statute, suitability petitions are for drugs that have a different active ingredient, route of administration, dosage form, or strength. (See 21 U.S.C. 355(j)(2)(C).) A person seeking marketing approval of a drug product that differs from the listed drug product only with respect to inactive ingredients is not required to submit a suitability petition. FDA also notes that § 314.94(a)(9)(ii) requires applicants to identify and characterize the inactive ingredients used in the proposed drug product, and this information should permit FDA to determine whether the different inactive ingredients affect the product's safety. If FDA determines that the inactive ingredients of the drug are unsafe, the agency will refuse to approve the ANDA. (See 21 U.S.C. 355(j)(3)(H); 21 CFR 314.127.)

As for proposed new combination drug products, the statute expressly authorizes petitions for drugs with one different active ingredient. The petitioner must provide information to show that the different active ingredient is "an active ingredient of a listed drug or a drug which does not meet the requirements of section 201(p)" (21 U.S.C. 355(j)(3)(C)(iii)(II)). Although the statute does not expressly require drug interaction data, it authorizes FDA to refuse to approve a petition if "investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients" or if a drug product containing a different active ingredient "may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application" (21 U.S.C. 355 (j)(2)(C)(i) and (j)(2)(C)(ii)). Thus, if the agency determines that the safety and effectiveness of a proposed combination drug product cannot be shown without drug interaction data, FDA will not approve the petition. FDA has, on its own initiative, revised the language in § 314.93(d) to clarify the circumstances under which a petitioner may identify more than one listed drug. The revised language corresponds more closely to the statutory language.

19. One comment suggested that the agency revise proposed § 314.93(d)(3) regarding proposed combination drug products with one different active ingredient. The proposed rule would require petitioners to provide information to show that:

> If the proposed drug product is a combination product with one different active ingredient, including a different ester or salt, from the reference listed drug, that the different active ingredient has previously been approved in a listed drug or is a drug that does not meet the definition of "new drug" in section 201(p) of the act.

The comment suggested that § 314.93(d)(3) be revised to state that ingredients listed as Category I (generally recognized as safe or generally recognized as effective) in a tentative final or final OTC monograph are "substitutable ingredients."

FDA declines to revise the rule as requested. The rule is consistent with section 505(j)(2)(A)(ii)(III) of the act, which states that the different active ingredient must be "an active ingredient of a listed drug or of a drug which does not meet the requirements of section 201(p) * * *." Therefore, in order to be a "substitutable ingredient," a Category I ingredient must be either an active ingredient of a listed drug or an active ingredient that does not meet the definition of a "new drug." An ingredient included in a final OTC drug monograph would be a "substitutable ingredient" because it does not meet the definition of a "new drug."

20. One comment asked FDA to accept petitions to submit an ANDA for a product whose labeling differs from the reference listed drug by being "more clear or offer better directions regarding how the drug should be taken."

FDA declines to accept the comment. Suitability petitions are for drugs that have a different active ingredient, route of administration, dosage form, or strength. (See 21 U.S.C. 355(j)(2)(C).) Labeling differences, therefore, are not proper subjects for a suitability petition.

FDA reminds applicants that the labeling for an ANDA product must be the same as the labeling for the listed drug product except for differences due to different manufacturers, exclusivity, etc. (See 21 U.S.C. 355(j)(3)(G).) An ANDA applicant who believes that the labeling for a proposed drug product should differ from that approved for the reference listed drug should contact FDA to discuss whether labeling for both generic and listed drugs should be revised.

21. One comment objected to proposed § 314.93(e)(1)(v) because FDA would refuse to approve a petition if the reference listed drug had been voluntarily withdrawn from sale and FDA had not determined whether the withdrawal was for safety or effectiveness reasons. The comment would revise the rule to require manufacturers to provide detailed reasons for withdrawing a drug product and, if FDA concluded that those reasons involved safety or effectiveness issues, require FDA to provide this information to prospective ANDA applicants or petitioners.

FDA declines to amend the rule as requested. The statute does not require FDA to determine why a listed drug was withdrawn from sale in every case, and the agency believes it would be impractical to do so. The agency discusses this subject in greater detail in its discussion of the comments to 21 CFR 314.151 through 314.152.

22. Five comments focused on the term "limited confirmatory testing" mentioned in the preamble to proposed § 314.93(e)(2). Proposed § 314.93(e)(2) stated that the phrase, "investigations must be conducted," meant "information derived from animal or clinical studies is necessary to show that the drug product is safe or effective." The

preamble to the proposed rule explained that:

> If preclinical or clinical data are needed to support safety, or if clinical data are needed to support the effectiveness of the requested change, then an abbreviated new drug application is not appropriate for the proposed drug product, and FDA will not approve a petition. However, under certain circumstances, data from limited confirmatory testing to show that the characteristics that make the proposed drug product different from the listed drug do not alter its safety and effectiveness may be accepted in a petition or as additional data to be included in an ANDA resulting from an approved petition.
>
> 54 FR 28872 at 28880.

One comment asked FDA to define "limited confirmatory testing." Two comments noted that the preamble to the proposed rule would permit limited confirmatory testing but that the rule itself would not approve a petition if animal or clinical studies are needed. The comments suggested revising the rule so a drug product "for which any testing other than bioavailability testing is required is ineligible for ANDA treatment." Two other comments said limited confirmatory testing would create a new class of applications or permit firms to avoid full NDA requirements; these comments would eliminate such testing or limit their use to "very rare circumstances."

As stated in the preamble to the proposed rule, by "limited confirmatory testing," FDA means "simple studies intended to rule out unlikely problems." (See 54 FR 28872 at 28880.) Such tests do not include animal or clinical studies whose information is necessary to show that the drug is safe or effective. (See 21 CFR 314.93(e)(2).) Thus, FDA does not intend to permit petitioners to substitute limited confirmatory testing for clinical studies or otherwise circumvent NDA requirements.

23. One comment objected to the language in proposed § 314.93(e)(3), which said FDA may "at any time during the course of its review of an abbreviated new drug application, request additional information required to evaluate the change approved under the petition." The comment argued that this language would permit FDA to revoke its approval of a petition even after an ANDA is submitted.

When read in its entirety, § 314.93(e)(3) states that when FDA approves a petition, the agency may describe what additional information, if any, will be required to support an ANDA for the drug product, and that this approval should not be construed as preventing FDA from requesting additional information to evaluate the ANDA. Thus, the provision concerns information needed to support approval of the ANDA rather than the information needed to evaluate the petition.

As for "revoking" approval of a suitability petition, FDA is amending § 314.93 by adding a new paragraph (f) to give the agency express authority to withdraw approval of a suitability petition if new information indicates that approval should be withdrawn. Such information can come from any source, including ANDA's submitted under the petition. This amendment will ensure that suitability petition approvals continue to reflect valid, scientific judgment and reasoning and prevent would-be ANDA applicants from relying on suitability petitions that, in light of new information, would not have been granted had the new information been available when the petition was under consideration.

Section 314.94—Content and Format of an Abbreviated Application

FDA received over 100 comments pertaining to ANDA format and content. Most recommended revisions or clarification while several expressed general agreement with specific provisions.

Table of Contents

24. One comment suggested that proposed § 314.94(a)(2), which would require the archival copy of an ANDA to contain a table of contents, be revised to require that both archival and review copies of an ANDA contain a table of contents.

Although the provision in question only pertains to archival copies of an application, FDA agrees with the comment and has amended § 314.94(d)(2) accordingly.

Basis for an ANDA Submission

25. Two comments addressed reference listed drugs under proposed § 314.94(a)(3)(i). The proposed rule would require an ANDA to contain "the name of the reference listed drug, including its dosage form and strength." The comments noted that the preamble to the proposed rule stated that the pioneer drug would "usually" be the reference listed drug, but, if more than one listed drug existed for the same drug product, the preamble recommended that applicants contact the Director of the Division of Bioequivalence before selecting a reference listed drug (54 FR 28880–28881). The comments asked FDA to explain how FDA determines which drugs should be reference listed drugs, and one comment proposed that the pioneer drug serve as the reference listed drug "unless there are sound scientific reasons for which a substitute may be preferred."

As stated above, FDA has revised the rule so that FDA will designate all reference listed drugs. Generally, the reference listed drug will be the NDA drug product for a single source drug product. For multiple source NDA drug products or multiple source drug products without an NDA, the reference listed drug generally will be the market leader as determined by FDA on the basis of commercial data. FDA recognizes that, for multiple source products, a product not designated as the listed drug and not shown bioequivalent to the listed drug may be shielded from direct generic competition. If an applicant believes that there are sound reasons for designating another drug as a reference listed drug, it should consult FDA. Once FDA designates that reference listed drug, that drug will continue to be the reference standard even if the drug is later replaced as the market leader. The Orange Book will identify all reference listed drugs, so applicants are no longer instructed to call the Director of the Division of Bioequivalence. FDA has, however, deleted the language regarding **Federal Register** notices from § 314.94(a)(3)(i). As discussed elsewhere in this rule, the agency no longer regards a DESI notice as a listed drug and will not accept an ANDA in the absence of a listed drug.

Active Ingredients

26. Two comments sought more exacting standards or requirements for establishing that a generic drug and a listed drug contain the "same" active ingredients. Proposed § 314.94(a)(5)(i) would require an ANDA to contain information to show that the active ingredient in a single-active-ingredient product to be "the same as that of the reference single-active-ingredient listed drug." One comment stated that the active ingredients in the proposed drug product must be identical to those in the reference listed drug and that blood level comparisons are inadequate to establish such identity. The comment added that the rule should provide technical or scientific criteria for determining whether two active ingredients are equivalent.

The second comment would require applicants to demonstrate that their active ingredients "exhibit the same physical and chemical characteristics, that no additional residues or impurities can result from the different manufacture or synthesis process; and that the stereochemistry characteristics

and solid state forms of the drug have not been altered."

Under the statute, an ANDA applicant must show that its active ingredient is the same as that in the reference listed drug (21 U.S.C. 355(j)(2)(A)(ii)). FDA will consider an active ingredient to be the same as that of the reference listed drug if it meets the same standards for identity. In most cases, these standards are described in the U.S. Pharmacopeia (U.S.P.). However, in some cases, FDA may prescribe additional standards that are material to the ingredient's sameness. For example, for some drug products, standards for crystalline structure or stereoisomeric mixture may be required. Should questions arise, an applicant should contact the Office of Generic Drugs to determine what information would be necessary to demonstrate that its active ingredient is the same as that in the reference listed drug.

As for possible impurities or residues in the ANDA product, ANDA applicants would be required to provide information on the drug substance and the drug product as part of the chemistry, manufacturing, and controls section of the application. (See 21 CFR 314.94(a)(9); 314.50(d)(1).) This would include information on impurities and residues. The "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances" suggests that impurities "should not only be detected and quantitated, but should also be identified and characterized when this is possible with reasonable effort." This guideline adds that "All major impurities should be individually limited. The maximum amount per unit dose of every individual impurity should be provided. If there is information on toxicity or information on toxic limits that have been set of these impurities, this information should be provided." If the manufacturing, packing, or processing controls cannot ensure the product's identity, strength, quality, and purity, or if the drug's composition is unsafe, FDA will not approve the ANDA. (See 21 U.S.C. 355 (j)(3)(A) and (j)(3)(H).)

27. One comment sought clarification of proposed § 314.94(a)(5)(ii)(A). That provision would require an ANDA for a combination drug product to contain information to show that the active ingredients are the same as those for the reference listed drug, or,

> * * * if one of the active ingredients differs from one of the active ingredients of the reference listed drug and the abbreviated application is submitted pursuant to the approval of a petition under § 314.93 to vary such active ingredient, information to show that the other active ingredients of the drug product are the same as the other active ingredients of the reference listed drug, information to show that the different active ingredient of another listed drug or of a drug which does not meet the definition of a "new drug" in section 201(p) of the act, and such other information about the difference active ingredient that FDA may require.

The comment asked FDA to clarify the phrase "such other information about the different active ingredient that FDA may require."

The phrase quoted by the comment reflects the statutory language at section 505(j)(2)(A)(ii)(III) of the Act. FDA has not requested any additional information from applicants under this authority, and cannot predict what type of information it would require. Nevertheless, the final rule keeps this language and will not foreclose its use.

Bioequivalence

FDA received nine comments on proposed § 314.94(a)(7). That section describes the kinds of information required to demonstrate bioequivalence.

28. One comment suggested that applicants be given the option of submitting a proposed bioavailability or bioequivalence study protocol for review and comment either as part of an ANDA or before submitting an ANDA so that applicants do not conduct questionable or unnecessary studies.

Since publication of the proposed rule, FDA has changed its policies regarding the submission of incomplete ANDA's. Under earlier policy, FDA permitted ANDA applicants to submit ANDA's with bioequivalence study protocols and to provide bioequivalence study data at a later date. This policy has resulted in a significant and unwarranted expenditure of resources in reviewing applications that had little potential for approval. FDA will therefore no longer accept an ANDA that does not contain complete bioequivalence study data if such data are required for approval. However, with respect to pre-ANDA submissions of bioequivalence protocols, FDA will continue, to the extent that time constraints and resources permit, to provide guidance on such protocols before an ANDA is submitted. Applicants wishing such guidance may submit requests for review of proposed protocols to the Director, Division of Bioequivalence. The Division will attempt to provide informal comments on such submissions as time and resources permit. The agency has also revised § 314.94(a)(7)(i) to delete the language concerning **Federal Register** notices. As stated earlier, the agency no longer regards a DESI notice as a listed drug and will not accept an ANDA in the absence of a listed drug.

29. One comment recommended that FDA give each holder of an NDA for an innovator drug an opportunity to comment on any bioequivalence study protocol proposed by an ANDA applicant if "nonabsorbed drugs" are involved. The comment would also establish deadlines for the NDA holder to respond to the protocol and for FDA to issue a decision.

FDA has considerable scientific expertise in the critical review of bioequivalence protocols. If additional expertise is necessary, the agency will seek advice from sources such as the Generic Drug Advisory Committee on an "as needed" basis. The agency also notes that, as a basic matter, giving NDA holders a role in reviewing the applications of potential competitors could create a conflict of interest and compromise an applicant's confidential information. Therefore, FDA is not adopting the comment.

30. One comment stated that an FDA request for additional information under proposed § 314.94(a)(7)(ii) should be made within 30 days after the initial submission of the ANDA. As drafted, proposed § 314.94(a)(7)(ii) would require an ANDA submitted under a suitability petition to vary an active ingredient to contain "the results of any bioavailability or bioequivalence testing required by the agency, and any other information required by the agency to show that the different active ingredient is of the same pharmacological or therapeutic class as that of the changed ingredient in the reference listed drug, and that the proposed drug product can be expected to have the same therapeutic effect as the reference listed drug."

FDA declines to accept the comment. If FDA determines, after receiving an ANDA that was submitted pursuant to an approved suitability petition, that the ANDA applicant must submit additional information, this determination represents a finding that the information is necessary to ensure that the proposed ANDA drug product has the same therapeutic effect as the reference listed drug. (See 21 U.S.C. 355(j)(2)(A)(iv).) The agency will not, therefore, forego requesting such information simply because a specific time period has expired. FDA will act on ANDA's as expeditiously as agency resources and priorities permit, but cannot guarantee that the agency will be able to identify, within 30 days, all instances where it needs to request information.

31. One comment interpreted proposed § 314.94(a)(7)(ii) to mean that

safety and efficacy studies could be required and asked FDA to state that a product requiring more than bioequivalence testing cannot be the subject of an ANDA.

FDA will not require safety and effectiveness investigations under § 314.94(a)(7)(ii). As stated in section 505(j)(2)(C) of the act and § 314.93(e)(1)(i), if clinical investigations are needed to establish a product's safety or effectiveness, that product is not suitable for approval under an ANDA. FDA does not, however, interpret this section to preclude the use of data to demonstrate whether a proposed drug product will have the same therapeutic effect as a reference listed drug.

FDA has, however, revised § 314.94(a)(7)(ii) to state that an ANDA submitted under an approved petition must contain the results of any bioavailability or bioequivalence testing or any other information required by FDA to show that the active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those in the reference listed drug and that the proposed drug product can be expected to have the same therapeutic effect as the reference listed drug. This change encompasses ANDA's for single-ingredient drug products submitted pursuant to an approved suitability petition. The proposed rule inadvertently omitted a reference to such ANDA's and unintentionally created a potential problem for some ANDA applicants. For example, if the approved suitability petition permitted a change in dosage form, it might be difficult for some applicants to demonstrate bioequivalence between the new dosage form and the dosage form of the reference listed drug, e.g., between a cream and a tablet. The change corrects this problem and corresponds to the statutory language in section 505(j)(2)(A)(iv) of the act.

32. Proposed § 314.94(a)(7)(ii)(A) stated that FDA would consider a proposed drug product to have the same therapeutic effect as a reference listed drug if the applicant provided information demonstrating that:

> There is an adequate scientific basis for determining that substitution of the specific proposed dose of the different active ingredient for the dose of the member of the same pharmacological or therapeutic class in the reference listed drug will yield a resulting drug product of the same safety and effectiveness.

One comment would delete the adjective "same" from the phrase "of the same safety and effectiveness" because "[i]t may not be possible to have exactly the same safety and effectiveness, for example, if a different active ingredient is included in a combination product and safety or efficacy is enhanced." The comment recommended replacing the words "of the same safety and effectiveness" with "whose safety and effectiveness have not been adversely affected."

FDA agrees and has revised the rule accordingly.

33. One comment suggested amending proposed § 314.94(a)(7)(iii) to state that waivers from the in vivo bioavailability or bioequivalence requirement are possible under 21 CFR 320.22. As drafted, proposed § 314.94(a)(7)(iii) made no reference to waivers.

FDA declines to adopt the suggestion. Section 314.94(a)(7), generally, and § 314.94(a)(7)(iii), specifically, do not require in vivo bioequivalence. The provisions state the statutory requirement that an ANDA contain information to show bioequivalence and that, if that information is obtained from an in vivo study, the applicant include in its application information about the analytical and statistical methods used and information to show that the study was conducted in compliance with 21 CFR parts 50 and 56. Information to show bioequivalence may, depending on the drug product, come from an in vivo or an in vitro study.

34. Two comments focused on institutional review board (IRB) and informed consent requirements at proposed § 314.94(a)(7)(iii). The proposed rule would have required a statement regarding compliance with the IRB and informed consent requirements at 21 CFR parts 56 and 50, respectively, for each in vivo bioequivalence study in an ANDA. One comment asked FDA to identify the party responsible for providing a statement on IRB review and informed consent. The comment suggested that the "sponsor," which FDA presumes is the ANDA applicant, make such statements only after the sponsor had conducted an "appropriate on-site inspection of the records and the informed consent process as the study is performed." The second comment suggested revising the regulation to identify the party making the statement. The comment explained that sponsors who have transferred their obligations to contract research organizations should be able to provide the names and addresses of such organizations rather than make the statements on IRB review and informed consent themselves.

FDA declines to accept the comments. The ANDA applicant is ultimately responsible for ensuring that the ANDA satisfies all statutory and regulatory obligations, including IRB review under 21 CFR part 56 and informed consent under 21 CFR part 50. This is true even if the ANDA applicant has elected to use a contract research organization to conduct the study. If an ANDA does not contain such a statement, FDA may refuse to receive it. (See § 314.101(b)(3); see also § 314.101(d)(7).)

Labeling

Proposed § 314.94(a)(8) set forth labeling requirements for ANDA's. The proposal would require applicants to provide copies of the currently approved labeling for the reference listed drug, labels and labeling for the proposed drug product, and a statement that the applicant's proposed labeling is the same as that for the reference listed drug except for certain differences, including, but not limited to, differences due to exclusivity or patent protection. The proposal, at § 314.94(a)(8)(iv), would also require applicants to provide a side-by-side comparison of the applicant's proposed labeling with the approved labeling for the reference listed drug. The proposed rule did not state how applicants could acquire copies of the reference listed drug's labeling, but the preamble said current approved labeling could be obtained under the Freedom of Information Act (FOIA) (54 FR 28872 at 28884).

35. Several comments stated that obtaining copies of drug labeling under FOIA would be time-consuming, difficult, or impractical. The comments suggested that FDA develop procedures to display such labeling or to provide them to applicants upon written or oral request. One comment also said that FDA should routinely provide ANDA applicants with updated labeling.

FDA disagrees that its FOIA system is inadequate for ANDA labeling purposes. The agency's FOIA system handles information requests in an orderly and expeditious manner. The procedure for requesting information is both simple and straightforward. (See 21 CFR 20.40.) Additionally, FDA regulations, in most instances, require the Freedom of Information Staff to respond to a freedom of information request within 10 working days. (See 21 CFR 20.41(b).) For these reasons, FDA declines to create an alternate system for providing drug labeling.

As for providing updated labeling information, the agency does not believe it is currently feasible to routinely provide updated labeling on all products eligible for ANDA's. The Office of Generic Drugs (OGD) encourages applicants to contact OGD before submitting an ANDA for advice on what labeling would be the most appropriate to use for its proposed product. Such

labeling can ordinarily be obtained from one or more of the following sources, including (1) OGD labeling guidance documents, (2) the innovator or generic drug product labeling from the product itself, (3) Physician's Desk Reference, (4) FDA's Freedom of Information Office, or (5) calling the Drug Information Services Branch directly at 301–443–3910. FDA also provides further guidance to an ANDA applicant after the applicant submits proposed labeling. After ANDA approval, FDA tracks the labeling status of the pioneer drug product and, if necessary, notifies ANDA holders when and how they must revise their labeling.

36. One comment asked FDA to clarify its policy regarding the use of the ANDA holder's name on the label and package insert when the ANDA holder neither manufactures nor distributes the drug product.

FDA's policy regarding the names on drug product labeling is set forth at 21 CFR 201.1 as authorized by section 502 of the act (21 U.S.C. 352). In general, § 201.1 states that, with few exceptions, no person other than the manufacturer, packer, or distributor may be identified on the label of a drug or drug product. The Orange Book discusses this subject in greater detail and recognizes that, under certain circumstances, the ANDA holder's name might not appear on the product's labeling. (See "Approved Drug Products with Therapeutic Equivalence Evaluations," pp. 1–3 (1991).)

37. One comment asked how ANDA applicants should present proposed labeling. The comment said that FDA should specify its exact requirements or permit applicants to submit labeling in any format they choose.

FDA believes that detailed instructions on the size and format of proposed labeling are not appropriate for this regulation. Applicants who have questions about the presentation of labeling in ANDA's should contact the Program Support Staff, Office of Generic Drugs, for guidance.

38. Proposed § 314.94(a)(8)(ii) would require ANDA applicants to provide copies of the label and labeling for the proposed drug product. Two comments suggested that FDA amend the rule to permit applicants to provide photographs of labeling rather than actual copies of the labeling when the label is printed on a tube or shipping carton.

FDA declines to accept the comment. Actual copies of tube labeling and other labeling help FDA determine the prominence of the information presented and whether the information is legible. These determinations cannot be easily made by the review of photographs. Ordinarily, however, FDA does not require submission of copies of shipping carton labeling as part of an abbreviated application.

39. Two comments opposed the requirement for a side-by-side comparison between the proposed ANDA drug product's labeling and the reference listed drug product's labeling under proposed § 314.94(a)(8)(iv). The comments said the comparison would be cumbersome and impractical, and suggested annotated changes or highlighted changes instead of comparisons.

In contrast, three comments supported side-by-side labeling but asked that ANDA holders be required to complete labeling revisions within 30 days of any change in the listed drug's labeling or to provide labeling comparisons every 6 months to ensure that the ANDA drug's labeling matched that of the listed drug. One comment said FDA should create a mechanism to compel ANDA holders to revise their labeling to conform to the listed drug product once the ANDA is approved.

The final rule retains the requirement of side-by-side labeling comparisons. Side-by-side comparisons enable FDA reviewers to readily identify differences between the ANDA applicant's and the innovator's product labeling. FDA does not believe that this requirement will impose a significant burden on ANDA applicants.

As for creating a mechanism to compel labeling revisions, section 505(e)(2) of the act authorizes the withdrawal of approval of an application if "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof." This provision applies to both ANDA and NDA drug products. Because an ANDA must have labeling that is the same as the reference listed drug under section 505(j)(2)(A)(v) of the act, FDA believes that a generic drug product approved on the basis of studies conducted on the listed drug and whose labeling is inconsistent with the listed drug's labeling might not be considered safe and effective for use under the conditions prescribed, suggested, or recommended in the listed drug's labeling. FDA, therefore, has revised § 314.150 to permit the agency to withdraw approval of an ANDA if the applicant fails to maintain labeling in compliance with the requirements of the act.

As for requiring ANDA holders to submit drug labeling at periodic intervals, FDA believes that the existing reporting requirements at 21 CFR 314.70 and 314.81 ensure that labeling changes are brought to FDA's attention in an appropriate and timely fashion. The agency will advise ANDA holders of changes to be made after approval, but postapproval changes resulting from the expiration of exclusivity or patent protection are the responsibility of the ANDA holder.

40. Two comments said the labeling provisions should be revised to permit ANDA applicants to deviate from the labeling for the reference listed drug to add contraindications, warnings, precautions, adverse reactions, and other safety-related information. One comment added that ANDA applicants should be allowed to delete some of the indications contained in the labeling for the reference listed drug.

FDA disagrees with the comments. Except for labeling differences due to exclusivity or a patent and differences under section 505(j)(2)(v) of the act, the ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval. Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart. (See 54 FR 28872 at 28884.) If an ANDA applicant believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised. After approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.

41. One comment suggested revising proposed § 314.94(a)(8)(iv) to exempt ANDA holders from being required to submit pharmacokinetic data to support new labeling unless the new labeling pertained to serious health or safety effects. The proposed provision stated that differences between an ANDA applicant's proposed labeling and the labeling approved for the reference listed drug may include, among other things, differences in pharmacokinetics. The comment explained that "insignificant labeling changes otherwise could become a tool to impede the ability of generics to compete, or force them to raise prices to the consumer in order to absorb the cost of additional, insignificant and, perhaps, unnecessary pharmacokinetic studies."

The comment misinterpreted the proposed requirement. The provision

does not impose a pharmacokinetic data requirement for all labeling changes. In fact, FDA believes that most labeling changes that do not involve serious health or safety effects will be acceptable without new pharmacokinetic data. However, FDA also believes that some labeling changes may be formulation-specific and that such changes may require additional pharmacokinetic data (e.g., addition of a food effect statement). FDA, therefore, reserves the right to examine such labeling changes on a case-by-case basis to determine whether additional pharmacokinetic data are necessary before the ANDA holder changes labeling.

42. One comment proposed revising the third sentence in proposed § 314.194(a)(8)(iv), which listed certain permissible labeling differences between the ANDA drug product and the reference listed drug, to read as follows:

> Such differences protected by patent or accorded exclusivity by 505(j)(4)(D) of the act between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

The comment explained that the revision would protect ANDA applicants from "a possible claim of inducement or infringement where a nonapproved, but patented, method of administration is discussed in the innovator's label" or the labeling refers to more than one method of use and "some but fewer than all of the methods of use are entitled to nonpatent exclusivity."

FDA agrees in part with the comment and has amended the provision to state that differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include omissions of an indication "or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act."

Chemistry, Manufacturing, and Controls

FDA received a number of comments on the chemistry, manufacturing, and controls section of an ANDA.

43. Many comments sought further definitions or explanations regarding ANDA chemistry, manufacturing, and controls documentation requirements, including information on technical details, such as determining the source of impurities, potential degradation, and test methodologies. Two comments asked FDA to develop guidelines on acceptable levels of preservatives and other inactive ingredients.

These comments raise technical questions that are beyond the scope of this rule. FDA has already issued a number of guidelines addressing many of the questions. These guidelines apply to both full and abbreviated applications, and a list of available guidelines may be obtained from CDER Executive Secretariat Staff, Center for Drug Evaluation and Research (HFD–8), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. FDA will consider the comments in determining whether to revise existing guidelines or to develop new guidelines.

44. Several comments objected to the provisions in proposed § 314.94(a)(9) requiring ANDA applicants to use the same inactive ingredients as the reference listed drug or to identify and characterize the differences between inactive ingredients. The comments stated that ANDA applicants might not know or might be unable to discover all inactive ingredients used in the reference listed drug. The comments suggested that FDA either not require that the inactive ingredients be the same or require the disclosure of the inactive ingredients used in the reference listed drug.

Because the labeling regulations do not require listing of inactive ingredients for drug products in an oral dosage form (see 21 CFR 201.100(b)(5)), ANDA applicants may be unable to discover what inactive ingredients were used in such drug products. Consequently, FDA has revised § 314.94(a)(9) to require ANDA applicants to include such a comparison only for drug products intended for parenteral use, ophthalmic or otic use, or topical use. ANDA applicants will be able to determine the inactive ingredients in reference listed drugs for these dosage forms because such ingredients are disclosed on the labeling. (See 21 CFR 201.100(b)(5).) For other drug products, FDA has revised § 314.94(a)(9)(ii) to require applicants only to identify and characterize the inactive ingredients in the proposed drug product and to provide information demonstrating that the inactive ingredients do not affect product safety.

45. Proposed § 314.94(a)(9)(iv) stated, in part, that:

> * * * an applicant may seek approval of a drug product (intended for ophthalmic or otic use) that differs from the reference listed drug in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product, except that in a product intended for ophthalmic use, an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the listed drug, e.g., by using a balanced salt solution as a diluent as opposed to an isotonic saline solution, or by making a significant change in the pH or other change that may raise questions of irritability.

(54 FR 28872 at 28923).

One comment objected to the example involving balanced salt solutions and isotonic saline solutions in proposed § 314.94(a)(9)(iv). The comment explained that changes in an ophthalmic buffer or tonicity agent from isotonic saline to balanced salt solutions do not raise serious safety questions, and FDA cannot presume that such changes are to claim a therapeutic advantage.

When read in its entirety, the second sentence in § 314.94(a)(9)(iv) simply states that an applicant whose product is intended for ophthalmic use cannot change a buffer or substance to adjust tonicity "for the purpose of claiming a therapeutic advantage over or difference from the listed drug * * *." The rule does not state that use of a balanced salt solution as opposed to an isotonic saline solution would be impermissible in itself or that FDA would presume such changes to be for claiming a therapeutic advantage. Determining whether the applicant claims a therapeutic advantage over or difference from the listed drug depends on the circumstances surrounding each case.

Samples

46. FDA received one comment regarding generic drug product samples under proposed § 314.94(a)(10). The proposed rule would require ANDA applicants to comply with the sampling provisions at 21 CFR 314.50 (e)(1) and (e)(2) but would not require ANDA applicants to submit samples until FDA requested them. The comment suggested revising the rule to require ANDA applicants to obtain samples and to retain them in their stability containers for all lots of a finished product. The comment added that FDA should "make itself available as a witness if requested for the distribution of samples to laboratories for bioavailability studies."

Under existing current good manufacturing practice (CGMP) regulations, manufacturers are already required to retain samples. (See 21 CFR 211.84 and 211.170.) FDA has also issued an interim rule that requires applicants who conduct in-house bioavailability and bioequivalence testing and contract laboratories who conduct such testing to

retain reserve samples of the drug products used to conduct the studies. The interim rule, which appeared in the **Federal Register** of November 8, 1990 (55 FR 47034), and existing CGMP regulations will help FDA ensure that the samples sent to laboratories match the drug product to be produced. Therefore, the suggestion that FDA be available to witness distribution of samples to laboratories is unnecessary. FDA anticipates publication of a final rule shortly.

Patent Certification

FDA received a number of comments regarding patent certifications under proposed § 314.94(a)(12). The agency is still examining these comments and will finalize the provisions for patent certification at a later date.

DESI Drugs

47. Two comments objected to the inclusion in proposed § 314.94(b) of DESI drugs in the ANDA regulations. The proposed rule would permit persons to file ANDA's for a duplicate of a drug product that is subject to the DESI review or a DESI-like review and also a listed drug. If the ANDA is for a drug product that is a duplicate of a drug product that is subject to the DESI review or a DESI-like review and not listed, the proposed rule would require applicants to comply with the conditions set forth in the applicable DESI notice or other notice with respect to conditions of use and labeling and the ANDA content and format requirements. One comment argued that the statute applies only to post-1984 ANDA's so including DESI drugs was inappropriate. The comment suggested deleting this provision but noted that "additional special considerations need to be recognized" when finalizing the rule because, for some DESI active ingredient categories, there is no readily identifiable pioneer NDA product. A second comment stated that, under proposed § 314.94(b)(2), DESI drugs cannot be reference listed drugs unless they are listed or the applicant has filed an application under section 505(b)(1) or (b)(2) of the act.

The ANDA provisions of the 1984 amendments are applicable to all generic drugs for which approval is sought after September 24, 1984, the date on which the statute was enacted. However, after careful consideration, FDA agrees that ANDA's are inappropriate if the drug product that is the subject of a DESI review or DESI-like review has not complied with the conditions for effectiveness set forth in a DESI notice or other notice. In the absence of an approved product that satisfies the conditions set forth in the DESI notice or other notice, there is no "listed drug" within the provisions of section 505(j)(6) of the act, and an ANDA cannot be submitted for that drug.

Therefore, FDA will no longer accept an ANDA for a DESI drug product when there is no listed drug for that product, and has deleted § 314.94(b)(2) entirely. An applicant seeking approval of a drug product covered by a DESI upgrade notice before a product is approved for safety and effectiveness under that notice should submit a 505(b)(2) application to the Office of Generic Drugs. Generally the 505(b)(2) application must contain the information specified in section 505(b)(2) of the act, except that the labeling must meet the conditions of use announced as effective in the relevant DESI upgrade notice. In satisfying the full reports of investigations requirement under section 505(b)(1)(A) of the act, the applicant may refer to the agency's conclusions in the DESI upgrade notice about the product's safety and effectiveness and must demonstrate that the proposed drug product is bioequivalent to the drug product that is the subject of the relevant DESI upgrade notice. The agency will generally employ the same mechanisms and standards in approving a section 505(b)(2) application for a DESI drug product that it would for and ANDA under section 505(j).

Section 314.96—Amending an Unapproved ANDA

FDA received a small number of comments concerning proposed § 314.96. The proposed rule would permit applicants to amend an ANDA that had been submitted, but not yet approved, to revise existing information or to provide additional information. The proposed rule also explained when an amendment might extend the review period.

48. One comment objected to a preamble statement which said "data from a bioequivalence study where only a protocol was contained in the original submission" could be an example of a major ANDA amendment. (See 54 FR 28872 at 28888.) The comment said that an ANDA application should be complete when submitted and not completed through amendments.

FDA agrees with the comment. Under current policy, FDA does not accept an ANDA that contains only a bioequivalance study protocol. This policy is consistent with the statutory provision requiring an ANDA to contain information showing that the applicant's drug product is, rather than "will be shown to be," bioequivalent to the reference listed drug. (See 21 U.S.C. 355(j)(2)(A)(iv).)

49. One comment asked whether ANDA applicants could amend applications without informing FDA of their intent to amend them or withdraw applications after receiving an approvable or not approvable letter.

Under 21 CFR 314.110(b), an ANDA applicant who has received an approvable letter must correct the deficiencies described in the approvable letter "by amendment within the specified time period" or FDA will refuse to approve the abbreviated application. The ANDA applicant may also ask the agency to provide an opportunity for a hearing. Under 21 CFR 314.120(b), an ANDA applicant who has received a not approvable letter must amend or withdraw the ANDA or notify FDA of an intent to file an amendment within 180 days after the date of the not approvable letter. Under 21 CFR 314.120(a)(3), an ANDA applicant may also ask the agency to provide an opportunity for a hearing. If an ANDA applicant fails to respond within 180 days to the not approvable letter, FDA will consider the ANDA applicant's failure to respond to be a request to withdraw the ANDA. Thus, an ANDA applicant that receives an approvable or not approvable letter may amend its ANDA without informing FDA of its intent to amend the ANDA. The regulations also do not require ANDA applicants to provide notice of intent to withdraw an ANDA.

50. Several comments discussed "major" and "minor" amendments in relation to proposed § 314.96(a)(2) and (a)(3). Proposed § 314.96 (a)(2) would permit FDA to extend the review period if the amendment contained significant new data requiring additional time for agency review. Proposed § 314.96(a)(3) would treat the submission of an ANDA amendment to resolve substantial deficiencies as set forth in a not approvable letter as an agreement between FDA and the applicant to extend the review period 120 days. Neither provision referred to "major" or "minor" amendments, but the preamble to the proposed rule explained that a major amendment would be one which required substantial review time. The preamble provided several examples of such major amendments, including amendments containing data from a new bioequivalence study or stability or sterility study submitted in support of a drug product reformulation or changes in the manufacturing or controls procedures.

One comment stated that an amendment, regardless of whether it

was a "major" or "minor" amendment, should not result in any extension of the review period if FDA had not begun to review the application. This comment also suggested that "minor" amendments, which it defined as requiring less than 8 hours of review time, only result in a 14-day extension to the review period.

FDA disagrees with the comment. A policy that would permit applicants to submit amendments containing significant data or information without extending the review period would encourage the submission of incomplete ANDA's and create new administrative problems between applicants and the agency. For example, disputes would arise as to whether an amendment had been submitted before review had begun or whether a particular FDA action constituted "review."

As for extension periods, FDA has decided not to adopt proposed § 314.96(a)(2). The agency found the proposed provision to be unfeasible and has decided to retain the concepts at § 314.60. Consequently, FDA has revised § 314.96(a)(2) to state that an amendment containing significant data or information requiring additional time for agency review will constitute an agreement by the applicant to extend the date by which the agency is required to reach a decision on the application. The revised paragraph states that FDA will ordinarily extend the review period "only for the time necessary to review the significant data or information," and this period will not exceed 180 days. This paragraph, as revised, is similar to the preexisting requirements under § 314.60 and encourages ANDA applicants to submit complete applications.

Proposed § 314.96(a)(2) also stated that FDA would notify an applicant of the length of the extension. The agency has decided not to adopt the notification provision. FDA's experience suggests that it is difficult and impractical to predict the length of an extension for an ANDA given the unpredictable nature of its workload. At the same time, FDA emphasizes that extensions under this paragraph will be "only for the time necessary to review the new information." The agency hopes to be able to limit extensions under § 314.96(a)(2), which applies to amendments submitted other than in response to a not approvable letter, to generally not more than 120 days if resources permit.

With regard to the comment regarding "minor" amendments, under current Office of Generic Drugs policy, FDA distinguishes between major and minor amendments only with regard to amendments submitted in response to a not approvable letter. These are covered under § 314.96(a)(3).

51. Three comments concerned extending the review period for amendments under proposed § 314.96(a)(3). One comment suggested that the extension be "not more than 120 days." Another comment said major amendments responding to FDA reviewers should not constitute an agreement to extend the review period. This comment added that if an extension were necessary, "it should not affect the entire ANDA, but only the discipline in which it is generated." The third comment objected to § 314.96(a)(3) entirely and claimed, without explanation, that it was inconsistent with the statute.

As stated above with regard to § 314.96(a)(2), FDA has decided against the adoption of proposed § 314.96(a)(3) and, instead, has revised § 314.96(a)(3) to state that the submission of an amendment containing significant data or information to resolve deficiencies in the application as set forth in a not approvable letter constitutes an agreement between FDA and the applicant to extend the review period. This paragraph, as revised, corresponds to similar requirements under § 314.60. The extension will only be for the time necessary to review the significant data or information and would not exceed 180 days.

FDA notes that under current Office of Generic Drugs policy, FDA distinguishes between major and minor amendments submitted in response to not approvable letters. (See memorandum issued July 11, 1991, from the Director, Office of Generic Drugs, to Office Division Directors, Deputy Division Directors, Associate Office Directors, and Branch Chiefs). FDA currently considers a minor amendment to be one that an experienced chemist reasonably can be expected to take less than 1 hour to complete the review. Under current policy, FDA commits to make every attempt to take action on a minor amendment within 60 days of its receipt, subject to applicable agency clearances such as a field inspection or microbiology consult.

Although the agency would like to be able to review all major amendments and applications within the 180-day period provided by statute, and would like to establish goals for reviewing these submissions in even shorter time periods, current resources do not provide a basis for establishing such goals for the foreseeable future. The Agency's goal at this time is to meet its obligations under the statute and to review these submissions as efficiently and as expeditiously as possible without affecting the scientific integrity of the review.

The agency disagrees, however, with the comments that would prevent the agency from extending the review period. FDA's experience indicates that some amendments that are intended to respond to not approvable letters can be extremely complex and present new information. If the agency could not extend the review period after receiving such amendments, the only practical recourse would be not to approve the application and have the applicant submit a new ANDA. This would be inefficient and wasteful, so § 314.96(a)(3) treats an amendment under this paragraph as an agreement to extend the review period. This permits both FDA and the applicant to continue working on the ANDA.

FDA emphasizes, however, that an applicant who receives a not approvable letter and wishes to submit an amendment to resolve the deficiencies identified in the not approvable letter should confine its amendment to the subjects discussed in the letter. Completely new information on topics not raised in the not approvable letter only prolongs FDA review.

FDA disagrees with the comment claiming that the provision is inconsistent with the statute. Under section 505(j)(4)(A) of the act, FDA must approve or disapprove an application within 180 days after its initial receipt or "within such additional period as may be agreed upon * * *." The statute clearly recognizes that deciding whether to approve an application may require more than 180 days.

52. One comment said FDA should, upon submission of an ANDA, notify the applicant of the date on which the agency would approve or not approve the ANDA. Alternatively, the comment would require FDA to review an ANDA once it had been submitted to determine whether the application may be received.

FDA declines to adopt the comment. Under § 314.101(b)(2), FDA will notify applicants, in writing, whether the agency will receive an ANDA. (Such written notice, however, is not provided when FDA receives an ANDA supplement.) FDA will not, however, create a deadline for informing applicants whether an ANDA is received because such deadlines would be impractical. FDA cannot predict the number of applications it will receive in any given period and must remain flexible to assign its staff to respond to agency demands and priorities. As for notifying applicants of the latest date on

which FDA should approve or not approve an ANDA, § 314.100(a) states that FDA will send an ANDA applicant an approval letter, approvable letter, or not approvable letter within 180 days of receipt of an ANDA.

Section 314.97—Supplements and Other Changes to an Approved Abbreviated Application

FDA received no comments on this provision and has finalized it without change.

Section 314.98—Postmarketing Reports

Proposed § 314.98 would require an applicant that has an approved abbreviated antibiotic application or approved ANDA to comply with adverse drug experience reporting requirements. Proposed § 314.98(c), however, would not require holders of approved ANDA's or abbreviated antibiotic applications to submit periodic reporting of adverse drug experiences "if no adverse drug experience reports have been received and no labeling changes have been initiated by the applicant during the reporting interval."

53. Several comments, however, said postmarketing report requirements should be the same for NDA and ANDA holders. One comment said FDA should require ANDA holders to submit a periodic report that would indicate whether a company had received any adverse drug experience reports during the reporting period.

After careful consideration, FDA has revised § 314.98 to require ANDA applicants to submit a periodic report of adverse drug experiences even if the ANDA applicant has not received any adverse drug experience reports or initiated any labeling changes. As revised, the requirement is identical to that imposed on NDA holders. Periodic reports by ANDA holders will help FDA determine whether ANDA products have appropriate labeling and ensure that no adverse drug experiences go unreported.

54. FDA, on its own initiative, has amended § 314.98(a) to require abbreviated antibiotic application and ANDA applicants to comply with the recordkeeping requirements under § 314.80. This change corrects an inadvertent omission from the original proposal.

Section 314.99—Other Responsibilities of an Applicant of an Abbreviated Application

FDA received no comments on this provision and has finalized it without change.

Section 314.100—Timeframes for Reviewing Applications and Abbreviated Applications; Section 314.101—Filing an Application and an Abbreviated Antibiotic Application and Receiving an Abbreviated New Drug Application

Proposed § 314.100 discussed timeframes for reviewing applications and abbreviated applications. In general, the proposed rule would have FDA review an application or abbreviated application and send the applicant an approval letter, approvable letter, or not approvable letter within 180 days of receipt of an application under section 505(b) of the act, or an ANDA under section 505(j) of the act, or an abbreviated antibiotic application under section 507 of the act. Proposed § 314.101 concerned the circumstances under which FDA would file an application and an abbreviated antibiotic application and receive an ANDA. FDA received several comments suggesting additional agency obligations when an application or abbreviated antibiotic application is filed and when an ANDA is received.

55. One comment wanted the agency to amend proposed § 314.100 to require FDA to acknowledge receipt of an application and to issue an application number. The comment suggested that this occur within 14 days after the application is submitted.

Section 314.101 states that FDA will notify applicants, in writing, whether an application or abbreviated application is filed or received. (See 21 CFR 314.101(a)(2) and (b)(2).) These letters should contain an application number. As noted in paragraph 52 above, FDA believes that establishing a fixed time period for determining whether an application may be received would be impractical considering the number of applications and supplements FDA receives. As a result, FDA declines to amend the rule as requested.

56. Two comments suggested that either proposed § 314.100 or § 314.101 be amended to have FDA expressly determine whether an ANDA is "received" within 30 days of its submission.

FDA declines to accept the comments. As stated earlier, FDA cannot predict how many applications will be submitted in a given period, so it must retain flexibility to respond to any demands imposed on the agency. Creating an additional 30-day deadline in the ANDA review process would limit that flexibility without any significant benefit to FDA or to applicants.

57. Another comment said proposed § 314.101(b) should not authorize FDA to determine whether an abbreviated application may be received.

FDA rejects this comment. By determining whether an application is "received," FDA encourages applicants to submit ANDA's that comply with statutory and regulatory requirements and are sufficiently complete for substantive review to begin. This conserves FDA resources by permitting FDA reviewers to devote their time to examining reviewable applications.

58. Two comments stated that an ANDA lacking bioequivalence or bioavailability information, completed bioequivalence studies, or stability data to support at least a 24-month expiration date should not be received.

As stated earlier, FDA no longer accepts an ANDA that lacks complete bioequivalence or bioavailability information at the time of its initial submission. Consequently, the agency has deleted § 314.101(d)(8), which pertained to ANDA's that did not contain the results of any required or completed bioequivalence or bioavailability study.

As for the comment suggesting that an ANDA lacking stability data to support at least a 24-month expiration date not be received, FDA declines to adopt the comment. Although most ANDA's contain such stability data, applicants have submitted and FDA has approved ANDA's containing stability data that support a different expiration date.

59. FDA received two comments on proposed § 314.101(e)(1). The proposed provision stated that FDA will refuse to file an application or abbreviated antibiotic application or consider an ANDA not to have been received if the drug product that is the subject of the submission "is already covered by an approved application or abbreviated application and the applicant of the submission is merely a distributor and/or repackager of the already approved drug product." One comment suggested that the first sentence be revised to state that FDA "may refuse to file" an application or abbreviated application if any of the listed conditions apply. The comment explained that FDA should have discretion to file an application, notwithstanding the existence of an approved application, when the applicant could justify the need for the duplicate application or abbreviated application. The second comment asked FDA to file duplicate ANDA's if two or more companies jointly develop the product or if an exclusive licensee or distributor seeks to file an ANDA with the licensor's consent.

Section 314.101(e)(1) was intended to prevent distributors from forcing FDA to

review applications for drug products that are already covered by approved applications. Reviewing an application is extremely time-consuming, and FDA's resources are limited. To permit applicants to force review of an application for a product that is already covered by an approved application would result in a severe drain on FDA resources to review duplicate applications, create duplicate product and patent listings in the Orange Book, and contribute to the agency's accumulation of applications. FDA did not, however, intend to apply this provision against companies that jointly develop a product. The agency, therefore, is amending § 314.101 to change the refusal in proposed § 314.101(e)(1) to accept duplicate applications to a discretionary refusal to accept duplicate applications under a new § 314.101(d)(8). FDA has also revised § 314.101(d)(8) to clarify that the agency may refuse to file an application or refuse to consider an ANDA to be received for a drug product when the application already has an approved application or abbreviated application for the same drug product.

Additionally, the agency has created a new § 314.101(d)(9) to clarify that the agency may refuse to file a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act.

60. One comment asked FDA to amend § 314.101(f)(2) to add time periods for setting a hearing date following ANDA disapproval and for issuing a decision on a hearing. The comment also requested procedures for appealing a disapproval that would give the applicant "immediate attention" and be considered to be "final agency action."

The regulation pertaining to not approvable letters to applicants, § 314.120, states that when the agency refuses to approve an application, abbreviated antibiotic application, or ANDA, it will give the applicant a written notice of an opportunity for a hearing under § 314.120(a)(3). Section 314.200 states that, if the Commissioner of Food and Drugs grants a hearing, the hearing will begin within 90 days after the expiration of the time for requesting the hearing unless the parties otherwise agree in the case of denial of approval, and as soon as practicable in the case of withdrawal of approval (§ 314.200(g)(5)). Thus, there is no need to amend § 314.101(f)(2) to set a hearing date.

FDA also declines to set a deadline for resolving hearings or appeals. The demands placed on the presiding officer and other FDA employees assigned to administrative hearings can be immense depending on, among other things, the number of documents submitted to the administrative record. A large administrative record, coupled with the other obligations placed on the agency's employees, makes a deadline for resolving these matters impractical.

Finally, the administrative hearing regulations contain procedures for appealing a disapproval (e.g., 21 CFR 10.33 and 10.35). Parties may also seek judicial review as provided in 21 CFR 314.235(b).

Section 314.102—Communications Between FDA and Applicants

FDA received four comments regarding communications between FDA and applicants under proposed § 314.102. The proposed rule was substantially similar to the existing provision at 21 CFR 314.102 with the exception of new language to account for abbreviated applications and the availability of conferences and meetings for abbreviated applications. Proposed § 314.102(b) said FDA reviewers would make every reasonable effort to inform applicants of easily correctable deficiencies found in an application or abbreviated application or whether the agency would need more data or information. Proposed § 314.102(c) provided for 90-day conferences "to inform applicants of the general progress and status of their applications, and to advise applicants of deficiencies which have been identified by that time and which have not already been communicated." These conferences would be available for applications for all new chemical entities and major new indications of marketed drugs. Proposed § 314.102(d) would provide end-of-review conferences "to discuss what further steps need to be taken by the applicant before the application or abbreviated application can be approved." Finally, proposed § 314.102(e) indicated that applicants could request other meetings to discuss scientific, medical, or other issues.

61. One comment would require FDA reviewers to call ANDA applicants before issuing deficiency letters. The comment claimed FDA reviewers misinterpret or misread applications and could resolve these misunderstandings without a deficiency letter if they called ANDA applicants.

FDA declines to adopt the comment. The agency fully intends to communicate with ANDA applicants to resolve issues that arise during the ANDA review process but believes that requiring FDA reviewers to call ANDA applicants would be impractical and an inefficient use of resources. Some issues cannot be resolved or adequately described in a telephone call.

62. One comment proposed amending § 314.102(d) to require FDA to hold an end-of-review conference within 30 days of the issuance of a not approvable letter. Two comments addressed meetings under proposed § 314.102(e). One comment would require FDA reviewers and chemists to meet with any applicant upon 30 days notice. Finally, another comment urged FDA to be "liberal and speedy in granting requests for meetings on issues that arise during the review process."

FDA declines to accept the comments. FDA will make every attempt to grant requests for meetings that involve important issues, but, due to limited resources and other demands on reviewers, will not conduct meetings on a regular basis. The agency reiterates that 90-day conferences are available "on applications for all new chemical entities and major new indications of marketed drugs" (21 CFR 314.102(c) (emphasis added)), and that end-of-review conferences are available on all applications and 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" (21 CFR 314.102(d)). Thus, for ANDA's, 90-day conferences will generally be unavailable, and end-of-review conferences will be given low priority.

FDA adds that ANDA applicants who do request a meeting are encouraged to submit an agenda of important issues in advance for FDA's consideration. This will permit the agency to focus on specific issues and conserve resources.

Section 314.103—Dispute Resolution

FDA received no comments on this provision and has finalized it without change.

Section 314.104—Drugs with Potential for Abuse

63. Only one comment addressed proposed § 314.104, which states that FDA will inform the Drug Enforcement Administration (DEA) when an application or abbreviated application is submitted for a drug that appears to have an abuse potential. The comment supported the rule but asked FDA to "ensure the confidentiality of any information, including even the fact that an application has been submitted prior to providing that information to DEA."

Section 314.104 simply reflects FDA's obligation, under 21 U.S.C. 811(f), to forward to DEA information on any drug having a stimulant, depressant, or

hallucinogenic effect on the central nervous system if "it appears that such drug has abuse potential." (See 21 U.S.C. 811(f).) FDA's disclosure of information to another Federal agency does not necessarily result in the public disclosure of that information. (See 21 CFR 20.85.) Indeed, the regulation on public disclosure of information at § 314.430 states that FDA will not publicly disclose the existence of an application or an abbreviated application before sending the applicant an approval letter unless the application or abbreviated application's existence has been previously publicly disclosed or acknowledged (21 CFR 314.430(b)). This includes data in an application or abbreviated application (21 CFR 314.430(c)). Disclosure of any trade secret information obtained under section 505 of the act is also prohibited by section 301(j) of the act.

Section 314.105—Approval of an Application and an Abbreviated Application

64. FDA received two comments on proposed § 314.105(d). Under that provision, FDA will approve an ANDA and send the applicant an approval letter if the agency finds none of the grounds for refusing ANDA approval to apply. Both supported the rule, but one comment said an approval letter should not raise any new issues "except on the data submitted in response to an approvable letter."

With the exception of editorial matters or other minor deficiencies in an ANDA, approval letters should not raise new issues for applicants to resolve. Therefore, the comment's suggestion is unnecessary.

FDA has, on its own initiative, clarified that an approval with a delayed effective date is tentative and does not become final until the effective date. The agency has also amended § 314.105(c) to state that an abbreviated application must meet statutory standards for manufacturing and controls, labeling, and "where applicable, bioequivalence." This change reflects the statutory requirements for an ANDA.

Section 314.110—Approvable Letter to the Applicant

FDA received seven comments regarding approvable letters to applicants under proposed § 314.110. The proposed rule stated that FDA would send applicants an approvable letter "if the application or abbreviated application substantially meets the requirements of this part and the agency believes that it can approve the application or abbreviated application if specific additional information or material is submitted or specific conditions * * * are agreed to by the applicant." Proposed § 314.110 (a)(1) through (a)(5) would give those submitting full or abbreviated antibiotic applications 10 days to respond to or act on an approvable letter, request a hearing, or agree to an extension of the review period. Under proposed § 314.110(b), FDA would send approvable letters to ANDA applicants only if the ANDA substantially meets FDA requirements and the agency believed that "it can approve the abbreviated application if minor deficiencies in the draft labeling are corrected and final printed labeling is submitted." The proposed rule did not give ANDA applicants a specific time period to respond to an approvable letter.

65. Two comments recommended revising proposed § 314.110(a)(3). That provision stated that an NDA applicant who receives an approvable letter may ask FDA to provide an opportunity for a hearing on the question of whether there are grounds for denying approval of the application under section 505(d) of the act. One comment urged FDA to provide an opportunity for a hearing to ANDA applicants. The second comment suggested revising the rule to provide hearing dates.

With respect to ANDA applicants, FDA is amending § 314.110(b) to permit ANDA applicants to request, within 10 days after the date of an approvable letter, that FDA provide an opportunity for a hearing. This is consistent with the opportunity for a hearing provided to applicants who receive a not approvable letter under § 314.120, although the agency believes that most issues raised by approvable letters should be capable of being resolved without a hearing. The agency is also amending § 314.110(a)(3) to note that abbreviated antibiotic applications applicants will have an opportunity to request a hearing under § 314.125. The proposed rule inadvertently omitted such language even though §§ 314.101 and 314.125 suggested that these applicants had an opportunity for a hearing.

As for providing hearing dates, FDA believes that amending the rule to provide hearing dates would be impractical. FDA's experience with scheduling administrative hearings shows that finding mutually acceptable hearing dates can be difficult, and the parties often request postponements even after a hearing date has been set.

66. Two comments suggested that FDA prescribe time limits for its review of amendments submitted in response to an approvable letter. One comment would require FDA to review an ANDA applicant's response to an approvable letter within 45 days. A second comment would require FDA to review an ANDA applicant's response within 90 days.

FDA declines to amend the rule as suggested. Under § 314.110(b), FDA will send an approvable letter to an ANDA applicant only if the ANDA meets regulatory requirements under 21 CFR part 314 and FDA "believes that it can approve the abbreviated application if minor deficiencies are corrected * * *." However, FDA's ability to review an applicant's response to an approvable letter can vary due to a number of factors, such as the reviewer's skill, speed, and work load, the quality of the amendment or submission, and the complexity of the issues. Thus, the final rule does not require the agency to review an applicant's response within a single, predetermined time period. Unless the applicant's response to the approvable letter contains significant data or information requiring an extension of the review period, FDA should complete, and has the goal of completing, most of these reviews before 60 days have expired.

67. Two comments asked FDA to clarify when it would issue an approvable letter to an ANDA applicant. Under proposed § 314.110(b), FDA would send an ANDA applicant an approvable letter "only if the application substantially meets the requirements of this part and the agency believes that it can approve the abbreviated application if minor deficiencies in the draft labeling are corrected and final printed labeling is submitted." One comment said an approvable letter should be appropriate for more than minor labeling changes, and should also be used for changes such as a change in U.S.P. requirements, or the addition or deletion of an alternate analytical method. The second comment asked FDA to define the phrase, "substantially meets the requirements of this part."

FDA agrees that approvable letters may be appropriate for more than minor labeling deficiencies. Consequently, the agency has revised the rule to state that minor labeling deficiencies are simply an example of the type of deficiencies for which an approvable letter may be appropriate.

As for the phrase, "substantially meets the requirements of this part," FDA means that, with the exception of minor deficiencies, the ANDA complies with the requirements under 21 CFR part 314.

Section 314.120—Not Approvable Letter to the Applicant

Proposed § 314.120 described the circumstances under which FDA would send a not approvable letter. Proposed § 314.120(a)(1) and (a)(2) would require applicants to amend, withdraw, or notify FDA of an intent to amend an application or abbreviated application. Proposed § 314.120(a)(3) would permit applicants to ask FDA to provide a hearing on the question of whether there are grounds for denying approval of the application under section 505(d) or (j)(3) of the act. Applicants would be required to respond to a not approvable letter within 10 days, except that ANDA applicants, under proposed § 314.120(b), would have 180 days to respond.

68. Most comments on proposed § 314.120 recommended changes to response times. One comment suggested amending § 314.120(a) to give applicants 30 days to respond to a not approvable letter. Two comments asked that the regulation require ANDA applicants to respond to a not approvable letter within 10 days rather than the 180 days given at § 314.120(b).

FDA declines to amend the rule as suggested by the comments. The comments did not contain any justification for revising the response times, and FDA sees no reason to do so.

69. One comment asked that proposed § 314.120(a)(3) be revised to make clear that ANDA and NDA applicants, upon receipt of a not approvable letter, have the right to request that the agency provide the applicant an opportunity for a hearing.

Section 314.120(a)(3) was intended to apply to both ANDA applicants and to NDA applicants. FDA, therefore, agrees with the comment and has revised the provision accordingly. FDA has also revised § 314.120(b) to clarify that an ANDA applicant must make its request for a hearing to FDA within 10 days after the date of the not approvable letter.

Section 314.122—Submitting an Abbreviated Application for, or a 505(j)(2)(C) Petition That Relies on, a Listed Drug That is no Longer Marketed

70. One comment suggested that the title be revised to read, "Submitting an Abbreviated Application for * * *" The comment said this change would be consistent with the definitions in § 314.3.

FDA agrees and has revised the title accordingly.

Section 314.125—Refusal to Approve an Application or an Abbreviated Antibiotic Application

FDA received no comments on this provision and has finalized it without substantive change.

Section 314.127—Refusal to Approve an Abbreviated New Drug Application

Proposed § 314.127 provided a list of reasons for refusing to approve an ANDA. In general, these reasons corresponded to those listed at section 505(j)(3) of the act.

71. One comment asked FDA to amend proposed § 314.127(c) to describe the type of information that it would require an ANDA applicant to submit to show that an active ingredient in an ANDA product is the same as the active ingredient in the reference listed drug. In brief, proposed § 314.127(c) would, in relevant part, have FDA refuse to approve an ANDA if there is insufficient information to show that the active ingredient(s) in the proposed drug product are the "same" as those in the reference listed drug.

Under 21 CFR 314.120, if FDA believes that an application is not approvable, it will notify the applicant in writing and describe the deficiencies in the application. Thus, in the situation described by the comment, the applicant could use the agency's written response to determine how it could demonstrate that its active ingredient is the same as that in the reference listed drug. Depending upon the circumstances, an applicant might find additional guidance in drug compendia or FDA guidelines. (See paragraph 26 above for a related comment.) The comment's suggestion, therefore, is unnecessary.

72. Proposed § 314.127(g) (now § 314.127(a)(7)) would permit FDA to refuse to approve an abbreviated application if information in the ANDA "is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug * * * except for changes required because of differences approved in a petition under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers." One comment said FDA should also require ANDA holders to obtain current labeling for the listed drug every 6 months and update their own labeling accordingly.

FDA has revised § 314.150 to require ANDA holders to maintain current labeling. Failure to do so may result in withdrawal of approval. FDA will not, however, require ANDA holders to obtain current labeling or to update their own labeling every 6 months because drug labeling does not change on a regularly scheduled basis.

73. A second comment recommended adding "or because of patent requirements" to the end of proposed § 314.127(g).

FDA agrees that a patent may be a valid reason for labeling differences between the reference listed drug and the ANDA drug product and that such differences should not be a basis for refusing to approve an ANDA. FDA has, therefore, revised the rule to indicate that labeling differences may also be due to patents or exclusivity. However, FDA cautions that it will not approve an ANDA with different labeling if the labeling differences affect product safety or efficacy. For example, if the patent protects information on a new dosing regimen and FDA concludes that the preexisting dosing regimen is unsafe, the different labeling for the proposed ANDA product would be grounds for refusing to approve the ANDA.

74. Proposed § 314.127(h)(1)(i) (now § 314.127(a)(8)(i)(A)) would permit FDA to refuse to approve an ANDA if FDA had any information that the proposed drug product's inactive ingredients are unsafe for use under the conditions prescribed, recommended, or suggested in the proposed drug product's labeling. Proposed § 314.127(h)(1)(ii) (now § 314.127(a)(8)(i)(B) would permit FDA to refuse to approve an ANDA if the proposed drug product's composition was unsafe under the conditions prescribed, recommended, or suggested in the proposed labeling because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included. One comment asked FDA to merge proposed § 314.127(h)(1)(i) and (h)(1)(ii) or to explain their differences.

FDA declines to revise the rule as suggested. Section 314.127(a)(8)(i)(A) and (a)(8)(i)(B) (proposed § 314.127(h)(1)(i) and (h)(1)(ii)) reflects the statutory language at section 505(j)(3)(H)(i) and (j)(3)(H)(ii) of the act, respectively, and serves different purposes. To illustrate, if FDA concluded that an inactive ingredient in a proposed ANDA product was unsafe, it could refuse to approve the ANDA under § 314.127(a)(8)(i)(A). If the proposed ANDA product involved a combination of inactive ingredients and the combination (as opposed to each inactive ingredient), either by the type or quantity of an inactive ingredient or the manner of formulation of the inactive ingredients into the product, shows that the product was unsafe, the refusal to approve the ANDA would occur under § 314.127(a)(8)(i)(B).

FDA received four comments on proposed § 314.127(h)(2) (now § 314.127(a)(8)(ii)). Under the proposal, FDA would consider a drug product's inactive ingredients or composition to be unsafe and refuse to approve an ANDA if, on the basis of information available to FDA, "there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raise serious questions of safety."

75. One comment said FDA must have a valid scientific reason, rather than a "reasonable basis" under proposed § 314.127(h)(2)(i), to conclude that an inactive ingredient raises "serious questions of safety." A second comment would replace the list of examples with a shorter, generalized list of safety questions.

If the reference to "valid scientific reason" is meant to suggest that the agency must have proof that a drug is unsafe before taking action, FDA disagrees with the comment. The preamble to the proposed rule explained how FDA concluded that section 505(j)(3)(H) of the act asuthorizes the agency to refuse to approve an ANDA if there is a reasonable basis to conclude that a drug product's inactive ingredients or composition raises serious questions about drug safety. In brief, section 505(e) of the act permits FDA to withdraw ANDA approval if there is evidence that the drug "is not shown to be safe." FDA can invoke this provision whenever there is a reasonable basis to conclude that a drug is unsafe even if the agency lacks proof that the drug is unsafe (54 FR 28902). In comparison, section 505(j)(3)(H) of the act authorizes FDA to refuse to approve an ANDA if "information submitted in the application or any other information available to the Secretary" shows that the drug's inactive ingredients or composition is unsafe. If FDA construed section 505(j)(3)(H) of the act as requiring proof that a drug product is unsafe before it could act, the agency would be obliged to approve an ANDA and then immediately initiate a proceeding to withdraw approval.

The U.S. Supreme Court has held that, in interpreting the act, it must be given " 'the most harmonious, comprehensive meaning possible' in light of the legislative policy and purpose," and must not " ' impute to Congress a purpose to paralyze with one hand what it sought to promote with the other.' " *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609, 631–632 (1973) (quoting *Clark* v. *Uebersee Finanz-Korp.*, 332 U.S. 480, 488–489). It would be inconsistent with these principles to interpret section 505(j)(3)(H) of the act as imposing a burden of proof on the agency that would require aproval of potentially unsafe drugs, or require a greater showing that a drug is not safe to disapprove a product than is required to withdraw approval of it. Therefore, FDA is interpreting that section as authorizing disapproval of an ANDA on the same basis as withdrawal under section 505(e)(2) of the act. Thus, an ANDA may be disapproved if there is a reasonable basis to conclude that one of its inactive ingredients or its composition raises serious questions about the drug's safety.

As for deleting the list of examples of changes that raise serious questions of safety, FDA has elected to amend the last sentence in § 314.127(a)(8)(ii)(A) (proposed § 314.127(h)(2)(i)) to read, "Examples of the changes that may raise serious questions of safety include, but are not limited to, the following." This amendment shows that the list of examples is not exhaustive and that the described changes do not automatically raise serious safety concerns that preclude ANDA approval.

The proposed rule listed several examples of changes that raise serious questions of safety. These examples included the "use of a controlled release mechanism never before approved for the drug" (proposed § 314.127(h)(2)(i)(E)) and "a change in composition to include a significantly higher concentration of one or more inactive ingredients than previously used in the drug product" (proposed § 314.127(h)(2)(i)(F)).

76. The third comment asked FDA to delete § 314.127(h)(2)(i)(E) and (h)(2)(i)(F) (now § 314.127(a)(8)(ii)(A)(*5*) and (a)(8)(ii)(B)(*6*)). The comment claimed that the use of a different controlled release mechanism or a change in composition to include a significantly higher concentration of one or more inactive ingredients should not preclude ANDA approval. The comment also suggested revising § 314.127(h)(2)(i)(F) to read, "A change in composition to include levels of an inactive ingredient for which published data may exist showing such levels to be unsafe."

FDA declines to accept the comment. When read in its entirety, proposed § 314.127(h)(2) states that FDA will consider a drug's inactive ingredients or composition to be unsafe and refuse to approve an ANDA if "there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raise serious questions of safety." FDA believes that such a reasonable basis may exist in the absence of published data. As the rule and the preamble to the proposed rule note, the examples listed in proposed § 314.127(h)(2)(i)(E) and (h)(2)(i)(F) simply illustrate FDA's experience. (See 54 FR 28903.) Thus, if the proposed drug product uses a delivery or release mechanism that has never been approved for that drug or contains a higher concentration of one or more inactive ingredients, FDA will not automatically refuse to approve the ANDA. Instead, FDA will refuse to approve the ANDA only if there is a reasonable basis to conclude that the change raises serious safety questions.

FDA has, however, revised the wording in the final rule at § 314.127(a)(8)(ii)(A)(*5*) to replace "a controlled release mechanism" with "a delivery or a modified release mechanism." This change reflects the agency's experience with novel delivery or modified release mechanisms and places emphasis on the delivery mechanism or modified release mechanism itself whereas the proposed rule could have been interpreted as focusing concern solely on controlled release mechanisms.

FDA has also revised the final rule at § 314.127(a)(8)(ii)(A)(*6*) to replace "higher concentration" with "greater content." This change recognizes the fact that minutely higher concentrations of one or more inactive ingredients do not always present serious questions of safety. In contrast, a drug that has a greater content of one or more inactive ingredients often presents serious questions of safety.

77. Proposed § 314.127(h)(2)(ii) (now § 314.127(a)(8)(ii)(B)) said FDA would consider an inactive ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and refuse to approve the ANDA unless "it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and, if it differs from the listed drug in a preservative, buffer, or antioxidant, the application contains sufficient information to demonstrate that the difference does not affect the safety of the drug product." A comment said that requiring information to show that changes in a preservative, buffer, or antioxidant do not affect safety was "unnecessarily excessive" because FDA knows commonly used preservatives, buffers, and antioxidants. The comment suggested revising the provision only to require submission of information on preservatives, buffers, and antioxidants that are not commonly used.

The statute authorizes the Secretary to withhold approval of an ANDA if

information submitted in the application or any other information available shows that "(i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included." (See 21 U.S.C. 355(j)(3)(H).) Thus, under the statute, the inquiry is not whether each preservative, buffer, and antioxidant is commonly used or known; instead, the inquiry is whether the preservatives, buffers, and antioxidants in the proposed drug product are safe under the conditions prescribed, recommended, or suggested in the labeling. Section 314.127(a)(8)(ii)(B) of this final rule reflects this concern, which is particularly acute for parenteral drug products. Therefore, FDA declines to revise the rule as suggested.

Section 314.150—Withdrawal of Approval of an Application or Abbreviated Application

Proposed § 314.150 concerned withdrawals of approvals of an application or abbreviated application under section 505(e) of the act. The proposed rule would permit FDA to withdraw approval of an application or abbreviated application under certain enumerated conditions, such as a finding that an imminent hazard to the public health exists (§ 314.150(a)(1)), or a finding that clinical data or other experience, tests, or scientific data show the drug is safe for use under the conditions of use approved in the application or abbreviated application (§ 314.150(a)(2)(i)).

78. Two comments said FDA should create a new provision authorizing the agency to withdraw an abbreviated application if the abbreviated application holder failed to modify its labeling to match labeling changes in the reference listed drug.

FDA agrees and has revised the rule accordingly. New § 314.150(b)(10) states that the ANDA applicant's failure to maintain drug labeling that is consistent with that of the listed drug may be grounds for withdrawing approval of the abbreviated application. The only exceptions to this withdrawal provision are labeling differences approved in the original ANDA or resulting from a patent issued on the listed drug after approval of the ANDA or from exclusivity accorded to the listed drug after approval. However, as noted in paragraph 39 above, if the agency concludes that a labeling difference resulting from patent protection or exclusivity compromises the safety or effectiveness of the generic drug product for any remaining conditions of use, FDA may withdraw approval of the ANDA under this provision.

Section 314.151—Withdrawal of Approval of an Abbreviated New Drug Application Under Section 505(j)(5) of the Act; Section 314.152—Notice of Withdrawal of Approval of an Application or Abbreviated Application for a New Drug

79. Proposed § 314.151 (concerning withdrawals of approval of ANDA's under 21 U.S.C. 355(j)(5)) did not provide ANDA applicants the opportunity for an oral hearing in the event of a withdrawal. FDA received seven comments claiming that ANDA applicants should have an opportunity for a hearing or an oral hearing when FDA proposes to withdraw approval of an application or abbreviated application. In general, the comments argued that ANDA applicants should have the opportunity for a hearing on due process grounds or to "assure fairness." One comment stated that section 505(e) of the act authorizes hearings whenever the agency proposes to withdraw approval of an application approved under section 505, and, therefore, ANDA holders were entitled to hearings because ANDA's are authorized by section 505(j) of the act. One comment, however, would deny ANDA applicants the opportunity for a hearing because an ANDA "is completely dependent on the continued approval of the reference listed drug" and the ANDA applicant "does not take the place of the listed drug applicant for purposes of exercising the right to protect that drug."

The statute and regulations contemplate withdrawing ANDA approval under two different circumstances. First, if FDA finds the ANDA product unsafe for use, lacks substantial evidence of effectiveness under the conditions of use prescribed, recommended, or suggested in its labeling, contains an untrue statement of material fact, or meets any of the other grounds for withdrawal under section 505(e) of the act, the agency may withdraw approval "after due notice and opportunity for hearing to the applicant" (21 U.S.C. 355(e)). For ANDA products, the regulations pertaining to a withdrawal of approval under section 505(e) of the act are at § 314.150. These regulations, contrary to some of the comments' assertions, do give ANDA holders an opportunity for a hearing on a proposal to withdraw approval of an ANDA to the extent that one or more of the grounds for withdrawal under section 505(e) of the act directly apply to the ANDA product. (See § 314.150 (a) and (b).)

The second situation in which ANDA approval may be withdrawn focuses on withdrawal of the listed drug rather than the ANDA product itself. Under section 505(j)(5) of the act, if the listed drug is withdrawn for safety or effectiveness reasons or any of the grounds listed in section 505(e) of the act, ANDA approval "shall be withdrawn or suspended * * *." The statute does not require FDA to give the ANDA holder an opportunity for a hearing before withdrawing or suspending ANDA approval.

The preamble to the proposed rule discusses this subject in greater detail. (See 54 FR 28904 through 28907.)

Notwithstanding the absence of a statutory requirement for a hearing, some comments claimed that due process requires FDA to give applicants an opportunity for an oral hearing for a proposal to withdraw ANDA approval under section 505(j)(5) of the act. FDA disagrees. As noted in the preamble to the proposed rule, courts have declared a "paper hearing" that provides adequate notice and a genuine opportunity to present one's case to be adequate. (See 54 FR 28904, July 10, 1989, and cases cited therein.) Section 314.151, therefore, gives ANDA holders a paper hearing and, if FDA cannot resolve the issues on the basis of the written submissions, permits FDA to hold a limited oral hearing. (See 21 CFR 314.151(b) and (c)(3).)

FDA believes these procedures are consistent with the statute and provide ANDA applicants adequate due process. Consequently, FDA declines to amend the rule as requested.

Section 314.153—Suspension of Approval of an Abbreviated New Drug Application; Section 314.161—Determination of Reasons for Voluntary Withdrawal of a Listed Drug

Proposed § 314.153(b) contained procedures for suspension of an ANDA when a listed drug is voluntarily withdrawn for safety or effectiveness reasons. The preamble to the proposed rule stated that "if a drug manufacturer withdraws a drug from the market which accounted for significant sales to that manufacturer, and there is no evidence to the contrary, it will be presumed that the withdrawal was for safety or effectiveness reasons" (54 FR 28907). The agency expressed its intent to employ the same presumption in applying proposed § 314.161.

80. FDA received eight comments on proposed §§ 314.153 and 314.161. All eight comments objected to the presumption stated in the preamble, but for different reasons. Many comments listed possible reasons why an NDA holder would voluntarily withdraw a drug for business or economic reasons alone. Some comments said ANDA holders should not have the burden of showing why the NDA holder voluntarily withdrew the reference listed drug. These comments would have FDA determine the reasons for a withdrawal or require the NDA holder to state its reasons for withdrawing the listed drug. Other comments said the presumption might adversely affect an NDA holder in product liability litigation. A minority of comments said the presumption's reference to "significant sales" was too vague and would produce different results between large and small firms; these comments argued that FDA, if it retained the presumption, should examine research and development expenses, percentage of a company's gross revenues, or the product's sales record for the previous year.

As stated in the preamble to the proposed rule, FDA is aware that companies may withdraw a drug from the market for reasons unrelated to the product's safety or effectiveness. (See 54 FR 28907.) The preamble also noted that FDA is not required to determine why a sponsor voluntarily withdrew a listed drug, and, considering the number of drugs withdrawn from the market every year, "it would be a needless expenditure of resources for the agency to determine the reason for each such withdrawal." Id. The comments have not raised any new issues or advanced any compelling justification for changing the presumption. The agency does note, however, that the presumption is a rebuttable one, and adds that the agency will, when the product is a top 200 drug (as reported in the April issue of Pharmacy Times which is based on data obtained from the National Prescription Audit conducted by IMS America, Ltd., Ambler, PA), and in other cases when it deems it to be necessary, contact the sponsor of the listed drug to inquire about the reasons for a voluntary withdrawal. In addition, the regulations do not prohibit NDA holders from disclosing their reasons for withdrawing a drug product from marketing, and FDA would consider that information in determining whether the withdrawal was for safety and effectiveness reasons. FDA would not consider the NDA holder's stated reasons for withdrawing a drug to be determinative because such remarks could be biased. Similarly, if an ANDA applicant can show that the reasons for withdrawal of the listed drug are not relevant to the safety or effectiveness of the ANDA drug product, the agency will not suspend ANDA approval. (See 21 CFR 314.153(b)(6).)

As for the comments suggesting alternatives to "significant sales," FDA agrees that the term may have different meanings to different companies, and will adopt a case-by-case approach when determining whether a product accounted for significant sales.

For these reasons, FDA has retained the presumption without change.

Section 314.160—Approval of an Application ar Abbreviated Application far Which Appraval Was Previausly Refused, Suspended, or Withdrawn; Section 314.162—Removal of a Drug Product fram the List; Section 314.200—Natice af Oppartunity far Hearing; Natice af Participation and Request for Hearing; Grant or Denial of Hearing

FDA received no comments on these provisions and has finalized them without change.

Sectian 314.430—Availability far Public Disclasure af Data and Infarmatian in an Applicatian or Abbreviated Application

81. FDA received four comments on proposed § 314.430. The proposal simply added the term "abbreviated application" to FDA's preexisting public disclosure policies and did not make any substantive changes to those policies. Two comments asked FDA to release a summary basis of approval (SBA) or permit ANDA sponsors to release their own SBA's when an ANDA is approved.

Section 314.430(e)(2)(ii) permits FDA to make an SBA available for public disclosure after FDA sends an approval letter. Hence, the comment's request to have FDA release an SBA is unnecessary. FDA also declines to amend the rule to permit sponsors to release their own SBA's. The rule pertains only to the release of information by FDA; sponsors are always free to disclose whatever truthful and nonmisleading information they wish about their own products.

82. One comment asked FDA to amend the rule to reveal the "presence" of a pending ANDA without any further identification so applicants could make "a more educated decision" about possible exclusivity.

While the comment has some merit, FDA declines to amend the rule at this time. The agency is reexamining certain aspects of its public disclosure policies, but notes that a suit to declare a patent to be invalid or not infringed by the manufacture, use, or sale of a drug product may suggest that an ANDA for that drug product has been submitted.

83. Another comment would give all NDA holders an opportunity to prevent disclosure of information for which they had previously requested confidentiality.

The act states that safety and effectiveness data submitted in an application under section 505(b) of the act and not previously disclosed to the public, "shall be made available to the public, upon request, unless extraordinary circumstances are shown." (See 21 U.S.C. 355(1).) Thus, the statute clearly favors disclosure of safety and effectiveness data except in limited situations. FDA is reexamining its policies with respect to section 505(1) of the act, and, until it completes its deliberations, declines to amend the rule as requested. FDA will continue its policy of consulting parties before disclosing information where the confidentiality of data and information is uncertain. (See, e.g., 21 CFR 20.45.)

Section 314.440—Addresses for Applications and Abbreviated Applications

FDA received no comments on this provision. However, due to reorganizations within FDA, the agency has revised the addresses to which abbreviated antibiotic application applicants and ANDA applicants are to send documents and correspondence.

Sectian 320.1—Definitions

Proposed § 320.1 defined "bioequivalence," in part, as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."

84. Six comments argued that § 320.1 should not include nonsystemically absorbed drug products and should not provide mechanisms other than blood level tests for bioequivalence. The comments noted that section 505(j)(7) of the act states that a drug shall be considered to be bioequivalent to a listed drug if, inter alia, "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental

conditions * * *." The comments claimed that this statutory provision precludes FDA from approving ANDA's for nonsystemically absorbed drug products because, the comments argued, the rate and extent of absorption of such products cannot be measured. One comment stated that in vivo bioavailability studies should be done to confirm that drugs not intended to be absorbed are not unintentionally absorbed.

The agency does not agree with the comments' interpretation of the statute. In 1977, FDA issued final regulations establishing the requirements for demonstrating the bioavailability and bioequivalence of drug products approved under both full new drug applications and ANDA's (21 CFR part 320). The definitions of "bioavailability" and "bioequivalence" adopted in those regulations were, in all pertinent respects, identical to the language used in section 505(j)(7) of the act. Although the 1977 regulations and the 1984 amendments to the act, which incorporate in the statutory provision on "bioequivalence" the language of those regulations, refer to "rate and extent of absorption," the 1977 regulations explicitly applies to drugs that are not intended for systemic absorption.

As originally proposed, the regulatory definition of "bioavailability" contained explicit reference to bioavailability studies other than systemic absorption studies. In the 1977 final rule, the Commissioner of Food and Drugs removed the references to the types of studies that can demonstrate bioavailability or bioequivalence as unnecessary and placed descriptions of appropriate studies in §§ 320.23, 320.24, 320.53, and 320.57. At the same time, the Commissioner of Food and Drugs specifically rejected a comment urging the definition of bioavailability to be restricted to products absorbed into the systemic circulation, stating that the concept of bioavailability applies to all drug products. (See 42 FR 1638 at 1639; January 7, 1977.)

All drug products must be absorbed through some physical barrier to reach the site of drug action, even if that absorption involves only dispersion into a body fluid pool or entry into surface cells. It is well established that drugs may be either locally or systemically absorbed, and nothing in the language of the statute requires that the absorption result in transit through cells or to the systemic circulation. Because Congress adopted the language of the 1977 regulations, and because the legislative history contains no evidence that Congress intended to exclude nonsystemically absorbed drugs from the coverage of the ANDA provisions of the 1984 amendments, FDA rejects the interpretation of section 505(j)(7)(B) of the act offered by these comments.

FDA also disagrees that blood levels are always appropriate or necessary measurements of bioequivalence. Bioequivalence can be established by pharmacodynamic measurement as well as by in vitro techniques and bioequivalence studies with clinical endpoints. The preferred method for establishment of bioequivalence, including the need to confirm that drugs not intended to be absorbed are not unintentionally absorbed, is determined on a case-by-case basis, depending on the drug under study.

Section 505(j)(6) of the act directs the Secretary to publish a list of all approved drugs for which ANDA's may be submitted and to state "whether in vitro or in vivo bioequivalence studies, or both such studies, are required * * *" (21 U.S.C. 355(j)(6)). In vitro studies are "test tube" studies intended to simulate drug effects in the human body, and are, by definition, indirect measurements of bioequivalence. Had Congress intended to require only direct measurements of the rate and extent of absorption in the human body, it would not have also permitted in vitro studies to satisfy the bioequivalence requirements. Thus, the statute permits and FDA's longstanding regulations provide for both indirect and direct measurements of bioequivalence applicable to nonsystemically absorbed drug products.

In summary, FDA's inclusion of nonsystemically absorbed drug products and inclusion of mechanisms other than blood level tests to establish the bioequivalence of drug products are consistent with the statute. The final rule therefore describes the types of studies that can be appropriately used to demonstrate bioavailability, and describes the bioavailability studies that are appropriate for nonsystemically absorbed durgs.

85. Proposed § 320.1 (a) and (e) defined "bioavailability" and "bioequivalence" using the phrase "active ingredient or active moiety." One comment proposed that the term "active moiety," which is used in proposed § 320.1 (a) and (e), does not find any statutory support and the regulations should instead use the statutory term "active ingredient." The comment's position was based on two court cases, *Abbott* v. *Young*, and *Glaxo* v. *Quigg*, which addressed the issue of using the term "active ingredient" as provided by statute instead of using the term "active moiety," with respect to the exclusivity provisions of title I and the patent term extension provisions of title II of the 1984 amendments, respectively. The comment stated that the courts concluded that there is a significant difference between the plain meaning of the statutory term "active ingredient" and the use of "active moiety." Equating the two is not permitted absent clear congressional intent. Thus, the comment argued that the term "active moiety" should not be used.

FDA disagrees with the comment. The court cases referred to by the comment are not relevant to FDA's use of the term "active moiety" in 21 CFR part 320. The statutory definition of "bioavailability" (section 505(j)(7)(A) of the act) uses the phrase "active ingredient or therapeutic ingredient," and the language on "bioequivalence" (section 505(j)(7)(B) of the act) uses the phrase "therapeutic ingredient." The agency is not substituting the phrase "active moiety' for the phrase "active ingredient." The phrase "active ingredient" remains in the definition of "bioavailability" in § 320.1(a) as in the statutory definition. The phrase "active ingredient" is not used in the statutory provision on "bioequivalence."

Congress clearly intended a meaning different from "active ingredient" by the term "therapeutic ingredient" or it would not have used both terms. The term "active moiety" refers to the molecule or ion in an active ingredient, excluding those appended portions of the molecule that cause the ingredient to be an ester, or a salt or other noncovalent derivative that is responsible for the physiological or pharmacological action of the ingredient. The agency believes that the term "active moiety" is more appropriate and has substituted this term for the term "therapeutic moiety" or "therapeutic ingredient" in defining the terms "bioavailability" and "bioequivalence."

86. One comment supported the proposed definition in § 320.1(e) of "bioequivalence" and opposed "across the board in vivo testing requirements." The comment asked FDA to "retain an open attitude toward the use of in vitro tests" and to have the regulations "reflect the fact that there are indeed other current and evolving methodologies, such as 'punch bioassays' and 'skin-blanching' tests, that will provide an equal measure of scientific comfort to demonstrate bioequivalence."

The final rule does not impose across-the-board in vivo testing requirements. With respect to drug products that are not included in the classes of drug

products described in § 320.22 for which the submission of evidence obtained in vivo is waived, FDA will consider requests for waiver of evidence obtained from in vivo testing on an individual basis. In addition, when other, more accurate, sensitive, and reproducible testing methods are not available, FDA will accept appropriately designed comparative clinical trials for purposes of demonstrating in vivo bioequivalence. Section 320.24 describes in vivo and in vitro testing approaches in descending order of accuracy, sensitivity, and reproducibility that are acceptable to FDA for determining the bioavailability or bioequivalence of a drug product.

87. The proposed definition of bioequivalence at § 320.1(e) provides that where there is an intentional difference in rate (e.g., in certain controlled release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient of moiety becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations, and is considered medically insignificant for the drug.

One comment suggested that the last sentence in § 320.1(e) be amended by replacing the conjunction "and" with "or." The comment also suggested that FDA define an "intentional difference" as one that involves the improvement of patient compliance or the manufacture of a more pharmaceutically elegant dosage form.

FDA declines to revise the definition as suggested by the comment. The use of the conjunction "and" in the regulation is consistent with statutory language in section 505(j)(7)(B)(ii) of the act. FDA also declines to define "intentional difference" as one that involves the improvement of patient compliance or the manufacture of a more pharmaceutically elegant dosage form because there may exist other valid reasons for altering rate, for example, to reduce toxic effects produced by high concentrations of a drug in an immediate release formulation.

88. Proposed § 320.1(e) defines bioequivalence to mean the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Several comments asked FDA to clarify the meaning of the phrase "significant difference" in the definition. Two comments understood "significant difference" to mean a "medically significant" or "therapeutically significant" difference. Other comments interpreted the phrase as meaning a statistically significant difference.

The determination of a significant difference requires first a judgment as to what difference in a bioequivalence parameter of interest is medically important and, second, a statistical analysis of data for the parameter to ensure that the difference determined to be important is not likely to be exceeded. Thus, based on clinical experience, the agency has developed statistical criteria for determining the bioequivalence of drug products. For example, there is a presumption that most drug products show no significant difference from the rate and extent of absorption of the listed drug and that the differences are unlikely to be clinically significant in patients when their absorption (AUC and C_{max}) is within 20 percent of the listed drug in normal subjects, and the probability that the results occurred by chance is less than 5 percent ($p<.05$).[1] In other words, unless there is a justification for different limits, the extent of absorption of the generic product must be not less than 80 percent, and not more than 120 percent, of the extent of absorption from the listed or innovator product. However, FDA will reexamine approval criteria for products falling outside the established statistical boundaries when applicants submit to FDA convincing evidence to establish a greater window of bioavailability or bioequivalence.

89. One comment asked FDA to clarify the difference between bioequivalence and therapeutic equivalence for products with intentional rate differences. Another comment argued that to rate some controlled release dosage form drugs as bioequivalent to an immediate release listed drug, but not as therapeutically equivalent, would create two subsets of bioequivalent products—one where products are therapeutically equivalent, and another where products are not therapeutically equivalent, leading to confusion in interchangeability.

Therapeutic equivalence was defined in the Federal Register of January 12, 1979 (44 FR 2932 at 2937). To be rated as therapeutically equivalent, drug products must be pharmaceutical equivalents—i.e., contain identical amounts of the same active drug ingredient in the same dosage form—and meet identical compendia or other applicable standards of identity, strength, quality, and purity; must not present a known or potential bioinequivalence problem (or, if so, must meet an appropriate bioequivalence standard); must be adequately labeled; and must be manufactured in compliance with the regulations governing CGMP's. The agency will approve certain products with intentional rate differences as bioequivalent and rate them as therapeutically equivalent provided that they are pharmaceutical equivalents and the difference in rate at which the active ingredient or moiety becomes available at the site of drug action is intentional, reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug (21 CFR 320.1 (e)).

The agency believes that it is appropriate to approve certain controlled release dosage form drug products that are pharmaceutical alternatives, for which bioequivalence can be demonstrated, even though products that are not pharmaceutical equivalents cannot be rated as therapeutically equivalent. The agency's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) does not rate these products as therapeutically equivalent; thus, FDA does not consider them interchangeable. Because pharmaceutical alternatives are listed

[1] See "Report by the Bioequivalence Task Force on Recommendations from the Bioequivalence Hearing Conducted by the Food and Drug Administration, September 29–October 1, 1986," report dated January 1988 (Ref. 1). "There was consensus at the Hearing that differences of less than 20% in AUC and Cmax between products in normal subjects are unlikely to be clinically significant in patients. * * * Under current review procedures, the 90% confidence interval for the ratio of the test product mean AUC to that of the innovator must lie entirely within the inverval (0.80, 1.20)." (Page 29.)

Attachment five to the Report by the Bioequivalence Task Force states "current practice is to carry out the two one-sided tests at the .05 level of significance."

Attachment ten to the Report by the Bioequivalence Task Force states "For approval in most cases, the generic manufacturer must show that a 90% confidence interval of the difference between the mean response of its product and that of the innovator is within the limits ± 20% of the innovator mean. * * * FDA should use the 90% confidence interval (i.e., two one-sided t-tests each at the .05 level of significance) to evaluate the difference between treatments."

See, also, Schuirmann (Ref. 2 at p. 676), "the common ± 20% criteria" and Nightingale and Morrison (Ref. 3 at p. 1200), "With very few exceptions, experts have concluded that differences of less than 20% in the mean AUC between brand name and generic copies are acceptable."

under separate headings, and because only products rated as equivalent under the same heading are interchangeable, there should be no confusion about their interchangeability.

90. One comment disagreed that a product whose absorption rate is intentionally different from the listed drug's absorption rate can nevertheless be bioequivalent. The comment cited nitroglycerine as a product whose absorption rate is critical to effectiveness. Another comment stated that the rate differences should not need to be intentional for these products to be bioequivalent.

Both the statute and the final rule consider a product with a different rate of absorption than the listed product to be bioequivalent to the listed product only if the difference in rate is (1) intentional, (2) reflected in the labeling, (3) not essential to the attainment of effective body concentrations on chronic use, and (4) considered to be medically insignificant. All four criteria must be met for a product with a different rate of absorption to be considered bioequivalent. Thus, a product cannot be rated as bioequivalent to a listed drug when there is a difference in rate of absorption that is not intended or when the difference in rate of absorption is medically significant.

91. One comment asked that FDA expand by example or therapeutic category the drugs that can differ in rate of absorption and still be bioequivalent.

The agency is unaware of any category of products that can differ in rate of absorption and still be considered bioequivalent. Because an intentional rate difference from the reference product would need to be shown to be medically insignificant, FDA believes that determinations of bioequivalence in such cases would need to be made on a case-by-case basis.

Section 320.21—Requirements for Submission of In Vivo Bioavailability and Bioequivalence Data

Proposed § 320.21 would revise FDA's existing requirements for submitting in vivo bioavailability data to include in vivo bioequivalence data.

92. One comment stated that § 320.21(b), which would require evidence of bioequivalence to be included in an ANDA, contradicts the agency practice of accepting applications containing only bioequivalence protocols.

As stated above at paragraph 28, FDA will only accept complete applications. Incomplete applications will not be accepted. Thus, § 320.21(b) of this rule is consistent with current agency practice.

93. Proposed § 320.21(c) would require any person submitting a supplemental application to include bioavailability or bioequivalence evidence if the supplemental application proposes: (1) A change in the manufacturing process; (2) a labeling change to provide for a new indication, if clinical studies are required to support the new indication, or (3) a labeling change to provide for a new dosage regimen or an additional dosage regimen for a special patient population, if clinical studies are required to support the new or additional dosage regimen. One comment suggested that § 320.21(c)(2) and (c)(3) apply only to supplements to applications submitted under section 505(b) of the act. A second comment recommended that § 320.21(c)(2) and (c)(3) be removed because, the comment declared, bioavailability or bioequivalence data should not be needed in addition to clinical studies.

FDA disagrees with the suggested changes. The regulation at § 320.21(c)(2) and (c)(3) applies to supplements to ANDA's approved under section 505(j) of the act as well as to supplements to NDA's approved under section 505(b). (Because such a supplement to an ANDA would require review of clinical data, FDA would treat it as a submission under section 505(b) of the act.) There are a number of reasons why the agency would want bioavailability or bioequivalence data to be included in a supplement for which clinical studies were being conducted. For example, when a supplement covers a new dosage regimen, the agency is concerned about the possibility of nonlinear kinetics. Likewise, for a new patient population, the agency is concerned about the way the drug is absorbed, distributed, and cleared by the body in the target population. Some supplements for a new labeling indication will be for drug products for which a bioavailability study was never performed. In addition, clinical studies are often not done using the final formulation, and the agency may need bioavailability or bioequivalence information on the final formulation. However, in vivo bioavailability or bioequivalence studies are not always needed, and paragrapohs (a)(2) and (b)(2) in § 320.21 provides for FDA to waive the requirement for in vivo studies based on the submission of adequate information.

94. Proposed § 320.21(g) would, under specific circumstances, require any person holding an approved full or abbreviated application to submit to FDA a supplemental application containing new evidence demonstrating in vivo bioavailability or bioequivalence. One comment asked that the information that would cause FDA to require new evidence demonstrating in vivo bioavailability or bioequivalence be made publicly available and that the source of such information be disclosed.

FDA's regulations governing public information are intended to "make the fullest possible disclosure of records to the public, consistent with the rights of persons in trade secrets and confidential commercial or financial information * * *" (21 CFR 20.20(a)). Publicly disclosable information includes information contained in citizen petitions as well as information submitted as part of an application under section 505(b) of the act. (See 21 CFR 10.20(j); 21 U.S.C. 355(l).) FDA will make every effort possible—consistent with its obligations to preserve certain trade secret and confidential commercial information—to make public any information it receives that would cause the agency to require new in vivo bioavailability or bioequivalence information.

95. One comment said that FDA should require retention of product samples tested for bioequivalence and that samples should be drawn from commercial-sized lots produced on the equipment that will be used to manufacture the marketed product.

FDA agrees in part with the comment. In the **Federal Register** of November 8, 1990 (55 FR 47034), FDA published an interim rule that requires retention of bioavailability and bioequivalence testing samples. The interim rule applies to manufacturers who conduct in-house bioavailability and bioequivalence tests and to facilities conducting such testing under contract for a drug manufacturer. FDA does not agree that bioequivalence studies need necessarily be conducted on commercial-sized lots if certain conditions are met. See Office of Generic Drugs Policy and Procedure Guide 22–90 (September 13, 1990).

Section 320.22—Criteria for Waiver of Evidence of In Vivo Bioavailability or Bioequivalence

Proposed § 320.22 would, among other things, revise the existing criteria for waiving evidence of in vivo bioavailability to include waivers of in vivo bioequivalence, delete automatic waivers of in vivo bioavailability for certain drug products, and remove the list of "bioproblem" drugs.

96. One comment argued that the statute prohibits a waiver of in vivo bioequivalence data. Another comment urged that § 320.22 be revised to waive in vivo bioequivalence requirements for

topically applied preparations and drug products that are oral dosage forms not intended to be absorbed.

Although the statute requires ANDA applicants to provide bioequivalence information (except where the ANDA is being submitted for a change in a listed drug for which a suitability petition has been granted), it does not require that bioequivalence be shown through in vivo methods. For example, section 505(j)(6)(A)(i)(III) of the act requires the Secretary to publish and make available to the public "whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications * * *." If ANDA applicants were limited to in vivo bioequivalence methods, the statutory reference to in vitro methods would be superfluous. FDA, therefore, disagrees with the comment that the statute prohibits waivers of in vivo methods for demonstrating bioequivalence.

FDA has removed the automatic waiver of evidence of in vivo bioavailability for topically applied preparations and oral dosage forms not intended to be absorbed because the agency believes in vivo bioavailability may be required for certain products. Variations in the manufacturing process used by each individual manufacturer may result in differences in the bioavailability of these drug products. While neither topical drug products nor oral dosage forms not intended to be absorbed are listed in the class of products whose bioavailability may be considered self-evident based on other data in the application, applicants of such products may nevertheless request a waiver of the requirements for in vivo data under § 320.22(a). The agency will review each product on a case-by-case basis to determine if an in vivo study is necessary.

97. One comment said the proposed rule would increase duplicative safety and efficacy tests and increase the time and expense of obtaining ANDA's by reverting to "across-the-board" in vivo study requirements. It argued that removing automatic waivers for topical and nonsystemically absorbed drugs would make it nearly impossible for an ANDA applicant to obtain marketing approval and impose new bioavailability standards that exceed the pioneer's testing requirements.

Although § 320.22, as revised, removes the automatic waiver for topical and nonsystemically absorbed oral dosage products, this change does not require applicants to submit evidence of in vivo bioavailability or in vivo bioequivalence in every case. The elimination of the automatic waiver for nonsystemically absorbed oral dosage products simply reflects FDA's view that requests for waiver of in vivo bioavailability and bioequivalence for these products need to be reviewed on a case-by-case basis. While the amendments may well increase the number of in vivo studies required, the regulation does permit applicants to request a waiver of the requirement for the submission of evidence in the form of in vivo bioavailability or bioequivalence data provided the product meets the criteria in § 320.22.

FDA concedes that the burden of showing bioequivalence may sometimes be comparable to, or perhaps even greater than, the pioneer's burden of showing bioavailability. In such cases, FDA believes that the additional data are needed to meet current standards for bioequivalence. FDA also notes that the generic company's burden is not likely to be nearly as great as the pioneer's burden of showing that a drug product is safe and effective for its proposed uses.

98. Under proposed § 320.22(b)(1), FDA would waive the requirement for submission of evidence obtained in vivo demonstrating the bioavailability or bioequivalence of drug products that are solutions for intravenous administration. The proposal stated that the in vivo bioavailability or bioequivalence of these drug products is "self-evident" provided that the drug products contain the same active and inactive ingredients in the same concentration as the listed drug product (21 CFR 320.22(b)(1)(ii)). Proposed § 320.22(c) would provide for a waiver of in vivo data requirement for those "parenteral drug products that are determined to be DESI-effective or that are shown to be identical in both active and inactive ingredient formulation" to a drug product that is currently approved in an NDA (provided that the drug is neither in suspension form, nor phenytoin sodium powder).

On its own initiative, FDA is revising § 320.22(b)(1)(i) to include solutions for all parenteral injections within its scope. As revised, the provision includes, among others, intraocular, intravenous, subcutaneous, intramuscular, intra-arterial, intrathecal, intrasternal, and intraperitoneal solutions intended for parenteral injection. The in vivo bioavailability or bioequivalence of any drug product in that class may be shown without in vivo data if the product contains the same active and inactive ingredients in the same concentration as a drug product that is a subject of an approved full new drug application. Because all parenteral solutions are now included at § 320.22(b)(1)(i), the agency has deleted § 320.22(c), which is no longer needed.

99. Proposed § 320.22(b)(3) would waive the requirement for submission of evidence obtained in vivo demonstrating the bioavailability or bioequivalence of a product that is an oral solution, elixir, syrup, tincture, or similar other solubilized form provided that it contains: (1) An active ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application; and (2) no inactive ingredient that may significantly affect absorption of the active ingredient or active moiety. One comment asked that ophthalmic and otic solutions be added to the class of products described in § 320.22(b)(3) whose bioavailability or bioequivalence is deemed self-evident.

Although FDA does not believe that the in vivo bioavailability or bioequivalence of otic and ophthalmic solutions can be considered self-evident based on compliance with the criteria described in § 320.22(b)(3), FDA does believe that it can assume the bioavailability or bioequivalence of an ophthalmic or otic product, if the product meets the criteria described in § 320.22(b)(1)(ii), i.e., the product contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application. The regulation is revised accordingly.

100. Two comments objected to the requirement in § 320.22(b)(1)(ii) that inactive ingredients be the same as those in the listed drug, arguing that some differences should be allowed and that ANDA applicants do not know the inactive ingredients in the listed drug.

FDA declines to accept the comment. The final rule requires drug products intended for parenteral injection to contain the same inactive ingredients in the same concentrations to obtain a waiver from the in vivo bioavailability or bioequivalence requirement because FDA cannot always predict the consequences of minor changes (e.g., in salt concentration). FDA believes this criterion is important to retain even when the necessary information is not freely available to ANDA applicants. FDA notes that under 21 CFR 201.100(b)(5) drug products for other than oral use must usually list the names of all inactive ingredients except flavorings, perfumes, and color additives. In addition, under 21 CFR 201.100(b)(5)(iii), a drug product, "if it is intended for administration by parenteral injection, (must list) the quantity or proportion of all inactive ingredients, except that ingredients added to adjust the PH or to make the drug isotonic may be declared by name

and a statement of their effect * * *." Thus, ANDA applicants should be able to determine the identity of inactive ingredients for all nonoral dosage forms and the quantity or proportion of inactive ingredients for many drug products, including all parenterals. In many other cases, the identity and quantity of inactive ingredients will be voluntarily disclosed on the listed drug's lable or otherwise ascertainable.

101. Proposed § 320.22(b)(3)(i) stated the conditions under which the bioavailability or bioequivalence of oral solutions, elixirs, syrups, tinctures, or similar products could be considered self-evident. One comment asked that § 320.22(b)(3)(i) be revised to include solutions for application to the skin.

The agency agrees that the in vivo bioavailability or bioequivalence of a solution for application to the skin may be considered self-evident, provided that it has the same active ingredients in the same concentration as the listed drug and no inactive ingredient or change in formulation that may significantly affect absorption of the active drug ingredient or active moiety. Therefore, the regulation at § 320.22(b)(3)(i) has been revised to include solutions for application to the skin. On its own initiative, FDA is revising § 320.22(b)(3)(iii) to make clear that the waiver in that section is conditioned on the applicant making no change in product formulation, including deletion of an inactive ingredient, that may significantly affect the absorption of the active drug ingredient or active moiety.

102. Existing § 320.22(d)(5) waives the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability of a drug product if the product contains the same active drug ingredient and is in the same strength and dosage form as a drug product that is the subject of an approved full or abbreviated new drug application, and both products meet an appropriate in vitro test. FDA proposed to remove this provision, stating that there was no evidence to show that in vitro data alone are regularly sufficient to assure bioequivalence. Three comments asked that existing § 320.22(d)(5) be retained. One comment contended that FDA had little evidence to show that in vitro data alone are not sufficient for the same product manufactured by the same sponsor.

FDA rejects these comments. The burden of showing that a new product is bioavailable or bioequivalent rests with the applicant. In general, the submission of in vivo data is required to support a new product unless there is a known in vivo/in vitro correlation, in which case in vitro data alone may be sufficient. Section 320.22(d) of this final rule lists certain classes of drug products whose bioavailability or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo. (In addition, FDA continues to waive in vivo data for certain drugs determined to be effective for at least one indication under the DESI program.) As FDA has no evidence to show that in vitro data alone are regularly sufficient to support the bioequivalence of any other drug classes, the agency believes that it is inappropriate to retain existing § 320.22(d)(5). Section 320.22(d)(5) is, therefore, removed.

103. One comment urged that existing § 320.22(d)(5) be retained as a mechanism for waiving in vivo data requirements for minor formulation changes, i.e., changes in colors or flavor. The comment stated that some FDA review divisions require new applications for products that contain a new flavor or color, and concluded that these newly formulated products are not eligible for the waivers described in proposed § 320.22(e)(4).

The comment is incorrect in assuming that products that are reformulated to contain a new flavor, color, or preservative are ineligible for waiver under proposed § 320.20(e)(4) (§ 320.20(d)(4) in this final rule). Such new formulations are eligible for waiver whether they are covered by a new application or by a supplement to an approved application.

104. Proposed § 320.22(e)(2) (§ 320.22(d)(2) in this final rule) would waive the requirement for the submission of in vivo bioavailability evidence if the drug product "is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval" and the bioavailability of the other drug product has been demonstrated, both drug products meet an appropriate in vitro test approved by FDA, and the applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients. One comment suggested that the agency revise § 320.22(e)(2) to include all dosage forms, including extended release dosage forms. A second comment asked FDA to extend the waiver to extended release capsules whose active ingredients are beaded materials.

The agency never intended to include extended release dosage forms, and has modified § 320.22(d)(2) to so state. The agency disagrees that it would be appropriate to grant waivers to all extended release dosage forms or to all extended release capsules whose active ingredients are beaded materials because the current state of science and technology does not always permit meaningful correlations between in vitro dissolution rates and the rate and extent of in vivo bioavailability for these products. FDA believes that waivers may be appropriate under some circumstances for certain beaded extended release dosage forms. Waivers are ordinarily granted for certain beaded dosage forms, where bioavailability has already been established and the only difference between the reference product and the drug under study is not in the type of bead, but in the quantity of beads. However, waivers will not be granted for beaded dosage forms with nonlinear kinetics because differences of minor therapeutic consequence at lower dose could become greatly exaggerated at higher doses. FDA will consider waiver requests for such products on an individual basis.

105. Proposed § 320.22(g) would permit FDA to require in vivo bioavailability or bioequivalence data if it determines that any difference between the drug product and a listed drug may affect the bioavailability or bioequivalence of the drug product. One comment asked that § 320.22(g) not be used unfairly by pioneer companies to remove generic applicants from the market by bombarding the agency with small bioequivalence changes.

This provision, renumbered § 320.22(f), if not intended and would not be implemented to give unfair marketing advantage to any particular manufacturers. Rather, it permits FDA to impose additional requirements to ensure the continued bioavailability or bioequivalence of a drug product.

Section 320.23—Basis for Demonstrating in Vivo Bioavailability or Bioequivalence

The proposed amendments to § 320.23 would, among other things: (1) Permit applicants whose drug products are not intended to be absorbed into the bloodstream to demonstrate bioavailability by measuring the rate and extent to which the active ingredient or active moiety was absorbed and became available at the site of drug action (§ 320.23(a)(1)); (2) state that statistical techniques used shall be of sufficient sensitivity to detect differences in rate and extent of absorption that are not attributable to subject variability (§ 320.23(a)(2)); (3) rephrase the conditions under which a drug product whose rate of absorption

differs from the reference listed drug can be considered bioavailable (§ 320.23(a)(3)); and (4) declare two drug products to be bioequivalent if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose (§ 320.23(b)).

106. One comment stated that proposed language in § 320.23(a)(2) on "differences in rate * * * of absorption" is ambiguous. The comment said the phrase could be interpreted to mean either differences in the "first-order micro-rate constant for absorption," or, alternatively, maximum concentration, C_{max}, and time to maximum concentration, T_{max}.

The comment correctly points out that the regulation does not specify how absorption rate should be measured. Because drug product parameters may vary, absorption parameters are determined based on the nature of the drug being evaluated.

Section 320.24—Types of Evidence to Establish Bioavailability or Bioequivalence

107. One comment asked that § 320.24 require that an applicant submitting an ANDA for a drug that has a significant difference in a pharmacodynamic parameter that is correlated with safety or therapeutic effect demonstrate that the difference is not clinically significant. The comment also asked that § 320.24 be revised to state FDA's willingness to accept in support of an ANDA pharmacodynamic evidence in lieu of pharmacokinetic profiles when one or more pharmacodynamic parameters correlate with a drug's therapeutic effect.

The ANDA process is intended to provide a rapid and efficient route for generic drug approval. Section 505(j)(7) of the act requires that FDA find a generic drug product to be bioequivalent to the reference listed drug if differences in their rates and extents of drug absorption fall within predetermined statistical limits.

Standards for determining bioequivalence for a product are intended to reflect the nature of the therapeutic response for that product. Once the therapeutic index has been determined, the equivalence of a product's therapeutic response can be measured via plasma drug concentrations, which are generally believed to provide a precise and accurate reflection of product performance. It is highly unlikely that a clinically significant difference in product safety and efficacy will exist for a product that meets an applicable bioequivalence standard. However, should postmarketing surveillance or other information suggest the possibility of therapeutic inequivalence, the approval criteria for that drug entity would be reevaluated.

In general, for systemically absorbed drugs, blood level profiles are a more sensitive index of rate and extent of drug delivery than pharmacodynamic measures. Therefore, except for cases where the agency has indicated otherwise, when blood levels of a drug are measurable, product bioavailability and bioequivalence will be based on pharmacokinetic rather than pharmacodynamic response.

108. Proposed § 320.24(a) stated that applicants should conduct bioavailability or bioequivalence studies "using the most accurate, sensitive, and reproducible approach * * *." One comment suggested that proposed § 320.24(a) be revised to state that applicants who have begun bioequivalence testing under an FDA guidance document would not have to recommence their studies if FDA's guidance changes in the interim.

FDA declines to adopt the comment. Generally, the agency will not ask an applicant to recommence a study that is conducted under an FDA guidance document. However, if new information suggests the need to reconsider agency guidance on study design, the agency will not be bound by that previous guidance. Therefore, under some important circumstances, it may be necessary for an applicant to recommence a study.

109. Proposed § 320.24(b) lists tests in descending order of accuracy, sensitivity, and reproducibility that are acceptable approaches for establishing the bioavailability and bioequivalence of a drug product. On its own initiative, the agency has added to the list of acceptable tests "currently available in vitro tests that ensure human in vivo bioavailability." The addition is intended for drug products determined to be effective under DESI for at least one indication that contain no active ingredients regarded as presenting either actual or potential bioequivalence problems or drug quality or standards issues. These products are coded "AA" in the list of "Approved Drug Products with Therapeutic Equivalence Evaluations." The agency has created new § 320.24(b)(5) to list these in vitro tests, and has renumbered proposed § 320.24(b)(5) as § 320.24(b)(6).

110. One comment questioned whether the three tests listed in § 320.24(b)(1) are themselves listed in descending order of accuracy, sensitivity, and reproducibility. The comment suggested that FDA renumber the approaches to make clear its intent.

The approaches in § 320.24(b)(1) are listed in descending order of accuracy, sensitivity, and reproducibility. This means that the approach under § 320.24(b)(1), is preferable to §320.24(b)(1)(ii), as the comment suggested. The agency believes the regulatory language clearly captures the agency's intent, and does not believe that renumbering the approaches is needed. The comment is therefore rejected.

111. Under proposed § 320.24(b)(1), one approach for demonstrating bioavailability or bioequivalence would be through "an in vivo test in humans in which the concentration of the active ingredient or active moiety and its active metabolites, in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time." One comment contended that measurement of active metabolites in an in vivo test should be the exception rather than the rule, and that measurement of metabolites should not be required where the activity of the metabolite is not well documented.

In general, the determination of whether a metabolite would be used in the assessment of a product's bioavailability or bioequivalence is dependent upon the pharmacokinetic characteristics of the drug (e.g., product input function, rate of metabolite formation, and half-lives of the various species). Section 320.24(b) has been revised to make clear that measurement of active metabolites will only be required when appropriate.

112. Two comments objected to the inclusion in the list of approaches to demonstrate the bioavailability or bioequivalence of a product of "well-controlled clinical trials that establish the safety and effectiveness of the product" (§ 320.24(b)(4)). The comments argued that clinical efficacy or safety trials to demonstrate bioequivalence are not bioequivalence determinations under the statute. The comments suggested that FDA should treat as a 505(b) application any ANDA application whose bioequivalency is based on clinical safety and effectiveness data.

As stated elsewhere in this document, the statute does not restrict applicants to a specific method for demonstrating bioequivalence. The preexisting regulations at 21 CFR 320.57 permitted applicants to demonstrate bioavailability and bioequivalence

through well-controlled clinical trials. The final rule retains this provision in § 320.24(b)(4). The measurement of clinical endpoints may thus be an acceptable approach for establishing bioequivalence for purposes of ANDA approval. The fact that clinical trial data are submitted to demonstrate bioequivalence does not therefore force FDA to convert an application to a section 505(b) application.

113. Proposed § 320.24(b)(4) would permit an applicant to determine a product's in vivo bioavailability or bioequivalence through well-controlled clinical trials or comparative clinical trials provided that analytical methods "cannot be developed" to determine that product's bioavailability or bioequivalence through the tests listed in proposed § 320.24(b)(1), (b)(2), or (b)(3). The comment urged that FDA replace the phrase "cannot be developed" with "have not been developed."

The agency declines to accept the comment because it believes that well-controlled clinical trials or comparative clinical trials should be used only when analytical methods cannot be developed using current technology. To allow clinical trials when such methods have not been developed would encourage their use in situations where technology exists, but an applicant prefers not to develop the analytical methods.

Section 320.30—Inquiries to FDA and FDA Review of Protocols

Proposed § 320.30 strongly recommends that persons planning to conduct a bioavailability or bioequivalence study submit proposed protocols to FDA for review before conducting the study. The proposed regulation also provided addresses for general inquiries on in vivo bioavailability and bioequivalence requirements.

114. Two comments suggest that the regulation be revised to require FDA to review proposed protocols. Two other comments asked that, to ensure timely review, the regulation specify a time period in which FDA must respond to requests for review of a protocol.

The agency will review proposed protocols as expeditiously as its resources and other agency demands permit. However, due to limited resources and an inability to predict the volume of submissions it will receive, the agency cannot commit itself to reviewing regularly all protocols nor will FDA specify a time limit for conducting reviews.

115. Proposed § 320.30(b)(2) would have FDA offer advice with respect to whether the reference material to be used in a proposed bioavailability or bioequivalence protocol is appropriate. One comment asked that, wher there are two approved innovator products that are not bioequivalent to each other, FDA allow either to be the reference standard.

As noted in the preamble to the proposed rule (54 FR 28872 at 28880), FDA intends to select reference listed drugs, which will be the reference standards for bioequivalence determinations. FDA will identify in future editions of the publication "Approved Drug Products with Therapeutic Equivalence Evaluations" the reference listed drug. By designating a single reference listed drug against which all generic versions must be shown to be bioequivalent, FDA hopes to avoid significant variations among generically quivalent drug products. Also, as stated previously, if an applicant believes that there are sound reasons for designating another drug as a reference listed drug, it should consult FDA.

Section 320.31—Applicability of Requirements Regarding an "Investigational New Drug Applicotion"

Proposed § 320.31 listed the types of bioavailability and bioequivalence studies for which an investigational new drug application (IND) would be required. Proposed § 320.31(a)(3) would require an IND if the in vivo bioavailability or bioequivalence study involved a cytotoxic drug product.

116. Two comments asked FDA to justify requiring IND's for cytotoxic products and for multiple-dose studies on controlled release products when no single-dose studies have been completed.

FDA believes that IND's are appropriate in these cases because of the potential risks to study participants through dose dumping or other toxic effects. FDA has 30 days to review and respond to an IND to determine potential safety problems and to assure effects that could threaten the safety of the subject participating in the study.

Section 320.51—Procedures for Establishing or Amending a Bioequivalence Requirement

117. The proposed rule proposed to remove 21 CFR 320.51, which sets forth procedurs for establishing or amending a bioequivalence requirement. One comment asked that § 320.51 not be removed because it requires FDA to use notice and comment rulemaking to develop or amend a bioequivalence requirement.

Because the 1984 amendments require that any new generic drug products be demonstrated to be bioequivalent to the reference listed drug (unless it is the subject of an approved ANDA suitaiblity petition), additional authority to impose bioequivalence requirements with respect to such products is not needed. However, on its own initiative, the agency has decided not to remove § 320.51 because it establishes a procedure to impose bioequivalence requirements on other classes of drug products not covered by the bioequivalence requirements in the 1984 amendments, including drug products not subject to premarket approval and drug products whose new drug status is not yet determined. In this final rule, § 320.51 has been redesignated and revised as § 320.32.

IV. Economic Assessment

FDA has considered the economic impact of this regulation which clarifies and facilitates the implementation of Public Law 98–417. Title I of Public Law 98–417 eliminated unnecessary regulatory barriers for generic drug products and has resulted in generic competition on many important post-1962 drugs. Generic drug sales account for a significant portion of total prescription drug sales, and many of these sales would not have occurred in the absence of Public Law 98–417.

Prior to the implementation of title I of Public Law 98–417, in order to market a generic post-1962 drug product, drug sponsors were required to duplicate the innovator's safety and efficacy testing and to submit a "duplicate" NDA. Under title I, sponsors no longer incur duplicate testing costs and are able to market generic products after submitting and gaining approval for an ANDA which does not include the duplicate testing requirement. The costs associated with preparing and submitting an ANDA are significantly lower than the costs for submitting duplicate NDA's for the same products.

The benefits of these implementing regulations for title I are twofold: (1) Savings to consumers who purchase generic post-1962 prescription drug products, and (2) savings to sponsors of generic drug products who submit ANDA's to the agency in order to gain approval to market their products. The consumer savings are the result of the increased availability of lower-priced generic drug products. As new generic products are made available annually (as their patents expire and generic drug products enter the marketplace) the savings to consumers should reach several billion dollars annually over the next 5 to 10 years. The savings to sponsors will vary depending on the

number of applications submitted annually. Small businesses will also be favorably affected because the barriers to market entry have been lowered thereby allowing these firms to enter the generic drug market without incurring duplicate safety and efficacy testing costs. Consequently, FDA concludes the benefits of these regulations implementing title I far exceed the costs. FDA also believes it has streamlined the ANDA process as much as possible thus minimizing the costs and maximizing the net benefits.

The regulatory framework for processing ANDA's under section 505(j) of the act has been in existence since the enactment of the Drug Price Competition and Patent Term Restoration Act in 1984. Thus, most required procedures and their associated economic consequences have been in effect since that time. This rule simply clarifies and facilitates the implementation of the act and will not affect the pace or magnitude of these impacts. Therefore, FDA concludes that this rule is not a "major rule" as defined by Executive Order 12291 and does not require a regulatory impact analysis. Similarly, the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities, and therefore does not require a regulatory flexibility analysis under the Regulatory Flexibility Act of 1980 (Pub. L. 96–354).

V. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does 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 1980

This final rule contains information collections which have been submitted for approval to the Office of Management and Budget under the Paperwork Reduction Act of 1980. The title, description, and respondent description of the information collection are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Title: Abbreviated New Drug Application Regulations.

Description: The information requirements collect information from persons who must obtain FDA approval prior to marketing generic copies of previously approved drugs. These persons must submit information in the form of applications, notices, and certifications. FDA will use the information submitted to determine whether the proposed generic drug is eligible for consideration, under what provisions an application would be considered, and whether the proposed drug is identical to the pioneer drug it purports to copy.

Description of Respondents: Businesses.

ESTIMATED ANNUAL REPORTING AND RECORDKEEPING BURDEN

Section	Annual number of respondents	Annual frequency	Average burden per response	Annual burden hours
314.50(g)	1	1	1 hour	1
314.50(i)	8	1	2 hours	16
314.50(j)	50	1	2 hours	100
314.54	10	1	80 hours	800
314.80, 310.305	40	1	8 hours	320
314.81	700	1	10 min.	119
314.93	82	1	10 hours	820
314.94	850	1	160 hours	136,000
314.110	10	1	40 hours	400
314.122, 314.161	1	1	10 hours	10
Total				138,586

There were no comments received on the Paperwork Reduction Act clearance submission or on the burden estimates. Therefore, no changes have been made to these burden estimates. However, the final rule does not finalize the provisions of the proposed rule on patent certification and market exclusivity. The agency has not included those estimates in the final rule.

VII. References

The following information has been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. "Report by the Bioequivalence Task Force on Recommendations from the Bioequivalence Hearing Conducted by the Food and Drug Administration, September 29–October 1, 1986," January 1988.

2. Schuirmann, D. J., "A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability," Journal of Pharmacokinetics and Biopharmaceutics, 15:6:657, 1987.

3. Nightingale, S., and J. Morrison, "Generic Drugs and the Prescribing Physician," Journal of the American Medical Association, 4:258:9:1200, 1987.

4. Skelly, J. P. et al., "Workshop Report: In Vitro and In Vivo Testing and Correlations for Oral Controlled/Modified-Release Dosage Forms," Pharmaceutical Research, 7:975–982, 1990.

List of Subjects

21 CFR Part 2

Administrative practice and procedure, Cosmetics, Drugs, Foods.

21 CFR Part 5

Authority delegations (Government agencies), Imports, Organization and functions (Government agencies).

21 CFR Part 10

Administrative practice and procedure, News media.

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 314

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

21 CFR Part 320

Drugs, Reporting and recordkeeping requirements.

21 CFR Part 433

Antibiotics, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 2, 5, 10, 310, 314, 320, and 433 are amended as follows:

PART 2—GENERAL ADMINISTRATIVE RULINGS AND DECISIONS

1. The authority citation for 21 CFR part 2 continues to read as follows:

Authority: Secs. 201, 301, 305, 402, 408, 409, 501, 502, 505, 507, 512, 601, 701, 702, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 335, 342, 346a, 348, 351, 352, 355, 357, 360b, 361, 371, 372, 374); 15 U.S.C. 402, 409.

2. Section 2.125 is amended by revising the introductory text of paragraph (h)(2) to read as follows:

§ 2.125 Use of chlorofluorocarbon propellants in self-pressurized containers.

* * * * *

(h) * * *

(2) An abbreviated new drug application conforming to § 314.94 of this chapter is acceptable in lieu of a full new drug application for any product included in the classes of products in paragraph (e) of this section if the product is one that is described under § 314.92 of this chapter. A finding has been made that an abbreviated new drug application may be submitted for the following products included in the classes of products listed in paragraph (e) of this section:

* * * * *

PART 5—DELEGATIONS OF AUTHORITY AND ORGANIZATION

3. The authority citation for 21 CFR part 5 continues to read as follows:

Authority: 5 U.S.C. 504, 552, App. 2; 7 U.S.C. 138a, 2271; 15 U.S.C. 638, 1261–1282. 3701–3711a; secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461); 21 U.S.C. 41–50, 61–63, 141–149, 467f, 679(b), 801–886, 1031–1309; secs. 201–903 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321–394); 35 U.S.C. 156; secs. 301, 302, 303, 307, 310, 311, 351, 352, 361, 362, 1701–1706, 2101 of the Public Health Service Act (42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 264, 265, 300u–300u–5, 300aa–1); 42 U.S.C 1395y, 3246b, 4332, 4831(a), 10007–10008; E.O. 11490, 11921, and 12591.

§ 5.80 [Amended]

4. Section 5.80 *Approval of new drug applications and their supplements* is amended in the introductory text of paragraph (c)(1) and paragraph (c)(2)(i) by removing "314.55, and 314.70" and replacing them with "314.70, and 314.94".

PART 10—ADMINISTRATIVE PRACTICES AND PROCEDURES

5. The authority citation for 21 CFR part 10 continues to read as follows:

Authority: Secs. 201–903 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321–393); 21 U.S.C. 41–50, 141–149, 467f, 679, 821, 1034, secs. 2, 351, 354–360F, 361 of the Public Health Service Act (42 U.S.C. 201, 262, 263b–263n, 264); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461); 5 U.S.C. 551–558, 701–706; 28 U.S.C. 2112.

6. Section 10.30 is amended by revising the introductory text of paragraph (e)(2) and by adding a new paragraph (e)(4) to read as follows:

§ 10.30 Citizen petition.

* * * * *

(e) * * *

(2) Except as provided in paragraph (e)(4) of this section, the Commissioner shall furnish a response to each petitioner within 180 days of receipt of the petition. The response will either:

* * * * *

(4) The Commissioner shall furnish a response to each petitioner within 90 days of receipt of a petition filed under section 505(j)(2)(C) of the act. The response will either approve or disapprove the petition. Agency action on a petition shall be governed by § 314.93 of this chapter.

* * * * *

7. Section 10.45 is amended by revising the introductory text of paragraph (d) to read as follows:

§ 10.45 Court review of final administrative action; exhaustion of administrative remedies.

* * * * *

(d) The Commissioner's final decision constitutes final agency action (reviewable in the courts under 5 U.S.C. 701 *et seq.* and, where appropriate, 28 U.S.C. 2201) on a petition submitted under § 10.25(a), on a petition for reconsideration submitted under § 10.33, on a petition for stay of action submitted under § 10.35, on an advisory opinion issued under § 10.85, on a guideline issued under § 10.90, on a matter involving administrative action which is the subject of an opportunity for a hearing under § 16.1(b) of this chapter, or on the issuance of a final regulation published in accordance with § 10.40, except that the agency's response to a petition filed under section 505(j)(2)(C) of the act and § 314.93 of this chapter will not constitute final agency action until any petition for reconsideration submitted by the petitioner is acted on by the Commissioner.

* * * * *

PART 310—NEW DRUGS

8. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 376); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

9. Section 310.305 is amended by revising paragraph (a), by removing the word "significant" in paragraph (b)(2), by revising the first sentence in paragraph (c)(4), and in paragraph (d)(1) by removing the words "(Drug Experience Report)" and replacing them with "(Adverse Reaction Report)" to read as follows:

§ 310.305 Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications.

(a) *Scope.* FDA is requiring manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved new drug or abbreviated new drug application to establish and maintain records and make reports to FDA of:

(1) All serious, unexpected adverse drug experiences associated with the use of their drug products;

(2) Any significant increase in the frequency of a serious, expected adverse drug experience; and

(3) Any significant increase in the frequency of therapeutic failure (lack of effect).

These reports will enable FDA to protect the public health by helping to monitor the safety of marketed drug products and to ensure that these drug products are not adulterated or misbranded.

* * * * *

(c) * * *

(4) Each person identified in paragraph (c)(1) of this section shall review periodically (at least once each year) the frequency of reports of adverse drug experiences that are both serious and expected and reports of therapeutic failure (lack of effect), received or otherwise obtained, and report any significant increase in frequency as soon as possible but in any case within 15 working days of determining that a

significant increase in frequency exists.

* * *

* * * * *

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

10. Part 314 is amended by redesignating existing Subparts C, D, E, and F as subparts D, E, F, and G, respectively, by adding new subpart C, consisting of §§ 314.92 through 314.99, by revising the table of contents with the authority citation continuing to read as follows:

Subpart A—General Provisions

Subpart B—Applications

Subpart C—Abbreviated Applications

Subpart D—FDA Action on Applications and Abbreviated Applications

Subpart E—Hearing Procedures for New Drugs

Subpart F—Administrative Procedures for Antibiotics

Subpart G—Miscellaneous Provisions

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 376).

§ 314.1 [Amended]

11. Section 314.1 Scope of this part is amended in paragraphs (a)(1) and (a)(2) by adding the phrase "or abbreviated application" after the word "application".

12. Section 314.3 is amended by revising paragraph (b) to read as follows:

§ 314.3 Definitions.

* * * * *

(b) The following definitions of terms apply to this part:

Abbreviated application means the application described under § 314.94, including all amendments and supplements to the application. "Abbreviated application" applies to both an abbreviated new drug application and an abbreviated antibiotic application.

Act means the Federal Food, Drug, and Cosmetic Act (sections 201–901 (21 U.S.C. 301–392)).

Applicant means any person who submits an application or abbreviated application or an amendment or supplement to them under this part to obtain FDA approval of a new drug or an antibiotic drug and any person who owns an approved application or abbreviated application.

Application means the application described under § 314.50, including all amendements and supplements to the application.

505(b)(2) Application means an application submitted under section 505(b)(1) of the act for a drug for which the investigations described in section 505(b)(1)(A) of the act and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

Approvable letter means a written communication to an applicant from FDA stating that the agency will approve the application or abbreviated application if specific additional information or material is submitted or specific conditions are met. An approvable letter does not constitute approval of any part of an application or abbreviated application and does not permit marketing of the drug that is the subject of the application or abbreviated application.

Approval letter means a written communication to an applicant from FDA approving an application or an abbreviated application.

Drug product means a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

Drug substance means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of

the human body, but does not include intermediates use in the synthesis of such ingredient.

FDA means the Food and Drug Administration.

Listed drug means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) or any current supplement thereto, as a drug with an effective approval. A drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that drug product.

Not approvable letter means a written communication to an applicant from FDA stating that the agency does not consider the application or abbreviated application approvable because one or more deficiencies in the application or abbreviated application preclude the agency from approving it.

Reference listed drug means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application.

Right of reference or use means the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary.

The list means the list of drug products with effective approvals published in the current edition of FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" and any current supplement to the publication.

13. Section 314.50 is amended by revising the first and fifth sentences in the introductory paragraph, paragraph (a)(2), and the second sentence in paragraph (c)(1), and by adding new paragraph (g)(3) to read as follows:

§ 314.50 Content and format of an application.

Applications and supplements to approved applications are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. * * * These include an application of the type described in section 505(b)(2) of the act, an amendment, and a supplement. * * *

(a) * * *

(2) A statement whether the submission is an original submission, a 505(b)(2) application, a resubmission, or a supplement to an application under § 314.70.

* * * * *

(c) *Summary.* (1) * * * The summary is not required for supplements under § 314.70. * * *

* * * * *

(g) * * *

(3) If an applicant who submits a new drug application under section 505(b) of the act obtains a "right of reference or use," as defined under § 314.3(b), to an investigation described in clause (A) of section 505(b)(1) of the act, the applicant shall include in its application a written statement signed by the owner of the data from each such investigation that the applicant may rely on in support of the approval of its application, and provide FDA access to, the underlying raw data that provide the basis for the report of the investigation submitted in its application.

* * * * *

14. New § 314.54 is added to read as follows:

§ 314.54 Procedure for submission of an application requiring investigations for approval of a new indication for, or other change from, a listed drug.

(a) The act does not permit approval of an abbreviated new drug application for a new indication, nor does it permit approval of other changes in a listed drug if investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the change. Any person seeking approval of a drug product that represents a modification of a listed drug (e.g., a new indication or new dosage form) and for which investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the changes may, except as provided in paragraph (b) of this section, submit a 505(b)(2) application. This application need contain only that information needed to support the modification(s) of the listed drug.

(1) The applicant shall submit a complete archival copy of the application that contains the following:

(i) The information required under § 314.50 (a), (b), (c), (d)(1) and (d)(3), (e), and (g).

(ii) The information required under § 314.50 (d)(2), (d)(4) (if an anti-infective drug), (d)(5), (d)(6), and (f) as needed to support the safety and effectiveness of the drug product.

(iii) Identification of the listed drug for which FDA has made a finding of safety and effectiveness and on which finding the applicant relies in seeking approval of its proposed drug product by established name, if any, proprietary name, dosage form, strength, route of administration, name of listed drug's application holder, and listed drug's approved application number.

(iv) If the applicant is seeking approval only for a new indication and not for the indications approved for the listed drug on which the applicant relies, a certification so stating.

(v) Any patent information required under section 505(b)(1) of the act with respect to any patent which claims the drug for which approval is sought or a method of using such drug and to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

(vi) Any patent certification or statement required under section 505(b)(2) of the act with respect to any relevant patents that claim the listed drug or that claim any other drugs on which investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug.

(2) The applicant shall submit a review copy that contains the technical sections described in § 314.50(d)(1) and (d)(3), and the technical sections described in § 314.50(d), (d)(4), (d)(5), (d)(6), and (f) when needed to support the modification. Each of the technical sections in the review copy is required to be separately bound with a copy of the information required under § 314.50 (a), (b), and (c) and a copy of the proposed labeling.

(3) The information required by § 314.50 (d)(2), (d)(4) (if an anti-infective drug), (d)(5), (d)(6), and (f) for the listed drug on which the applicant relies shall be satisfied by reference to the listed drug under paragraph (a)(1)(iii) of this section.

(b) An application may not be submitted under this section for a drug product whose only difference from the reference listed drug is that:

(1) The extent to which its active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug; or

(2) The rate at which its active ingredient(s) is absorbed or otherwise made available to the site of action is

unintentionally less than that of the reference listed drug.

§ 314.55 [Removed]

15. Section 314.55 *Abbreviated application* is removed.

§ 314.56 [Removed]

16. Section 314.56 *Drug products for which abbreviated applications are suitable* is removed.

17. Section 314.60 is amended by redesignating the existing paragraph as paragraph (a) and by revising the first sentence, and by adding a new paragraph (b) to read as follows:

§ 314.60 Amendments to an unapproved application.

(a) Except as provided in paragraph (b) of this section, the applicant may submit an amendment to an application that is filed under § 314.100, but not yet approved. * * *

(b)(1) An unapproved application may not be amended if all of the following conditions apply:

(i) The unapproved application is for a drug for which a previous application has been approved and granted a period of exclusivity in accordance with section 505(c)(3)(D)(ii) of the act that has not expired;

(ii) The applicant seeks to amend the unapproved application to include a published report of an investigation that was conducted or sponsored by the applicant entitled to exclusivity for the drug;

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

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

(2) The submission of an amendment described in paragraph (b)(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. The amendment will be considered a resubmission of the application, which may not be accepted except as provided in accordance with section 505(c)(3)(D)(ii) of the act.

18. Section 314.70 is amended by adding new paragraph (e) to read as follows:

§ 314.70 Supplements and other changes to an approved application.

* * * * *

(e) *Patent information.* The applicant shall comply with the patent information requirements under section 505(c)(2) of the act.

19. Section 314.71 is amended in paragraph (b) by revising the first sentence to read as follows:

§ 314.71 Procedures for submission of a supplement to an approved application.

* * * * *

(b) All procedures and actions that apply to an application under § 314.50 also apply to supplements, except that the information required in the supplement is limited to that needed to support the change. * * *

* * * * *

20. Section 314.80 is amended by removing the word "significant" in the definition of "Adverse drug experience" in paragraph (a), by revising paragraph (b), the first sentence in paragraph (c)(1)(ii), and the last sentence in paragraph (d)(1) to read as follows:

§ 314.80 Postmarketing reporting of adverse drug experiences.

* * * * *

(b) *Review of adverse drug experiences.* Each applicant having an approved application under § 314.50 or, in the case of a 505(b)(2) application, an effective approved application, shall promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.

(c) * * *

(1) * * *

(ii) The applicant shall review periodically (at least as often as the periodic reporting cycle) the frequency of reports of adverse drug experiences that are both serious and expected and reports of therapeutic failure (lack of effect), regardless of source, and report any significant increase in frequency as soon as possible but in any case within 15 working days of determining that a significant increase in frequency exists. * * *

* * * * *

(d) *Scientific literature.* (1) * * * The 15-day reporting requirements in paragraph (c)(1)(ii) of this section (i.e., a significant increase in frequency of a serious, expected adverse drug experience or of a therapeutic failure) apply only to reports found in scientific and medical journals either as the result of a formal clinical trial, or from epidemiological studies or analyses of experience in a monitored series of patients.

* * * * *

21. Section 314.81 is amended by adding new paragraph (b)(3)(iii) to read as follows:

§ 314.81 Other postmarketing reports.

* * * * *

(b) * * *

(3) * * *

(iii) *Withdrawal of approved drug product from sale.* (*a*) The applicant shall submit on Form FDA 2657 (Drug Product Listing), within 15 working days of the withdrawal from sale of a drug product, the following information:

(*1*) The National Drug Code (NDC) number.

(*2*) The identity of the drug product by established name and by proprietary name.

(*3*) The new drug application or abbreviated application number.

(*4*) The date of withdrawal from sale. It is requested but not required that the reason for withdrawal of the drug product from sale be included with the information.

(*b*) The applicant shall submit each Form FDA–2657 to the Drug Listing Branch (HFD–334), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(*c*) Reporting under paragraph (b)(3)(iii) of this section constitutes compliance with the requirements under § 207.30(a) of this chapter to report "at the discretion of the registrant when the change occurs."

* * * * *

22. Subparts C, D, E, and F are redesignated as Subparts D, E, F, and G, respectively, and new Subpart C, consisting of §§ 314.92 through 314.99, is added to read as follows:

Subpart C—Abbreviated Applications

§ 314.92 Drug products for which abbreviated applications may be submitted.

(a) Abbreviated applications are suitable for the following drug products within the limits set forth under § 314.93:

(1) Drug products that are the same as a listed drug. A "listed drug" is defined in § 314.3. For determining the suitability of an abbreviated new drug application, the term "same as" means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except that conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted. If a listed drug has been voluntarily withdrawn from or not offered for sale by its manufacturer, a person who wishes to submit an abbreviated new

drug application for the drug shall comply with § 314.122.

(2) Drug products that are duplicates of, or that meet the monograph for, an antibiotic drug for which FDA has approved an application.

(3) Drug products that have been declared suitable for an abbreviated new drug application submission by FDA through the petition procedures set forth under § 10.30 of this chapter and § 314.93.

(b) FDA will publish in the list listed drugs for which abbreviated applications may be submitted. The list is available from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402, 202–783–3238.

§ 314.93 Petition to request a change from a listed drug.

(a) The only changes from a listed drug for which the agency will accept a petition under this section are those changes described in paragraph (b) of this section. Petitions to submit abbreviated new drug applications for other changes from a listed drug will not be approved.

(b) A person who wants to submit an abbreviated new drug application for a drug product which is not identical to a listed drug in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one of the active ingredients in a listed combination drug, must first obtain permission from FDA to submit such an abbreviated application.

(c) To obtain permission to submit an abbreviated new drug application for a change described in paragraph (b) of this section, a person must submit and obtain approval of a petition requesting the change. A person seeking permission to request such a change from a reference listed drug shall submit a petition in accordance with §10.20 of this chapter and in the format specified in § 10.30 of this chapter. The petition shall contain the information specified in § 10.30 of this chapter and any additional information required by this section. If any provision of § 10.20 or § 10.30 of this chapter is inconsistent with any provision of this section, the provisions of this section apply.

(d) The petitioner shall identify a listed drug and include a copy of the proposed labeling for the drug product that is the subject of the petition and a copy of the approved labeling for the listed drug. The petitioner may, under limited circumstances, identify more than one listed drug, for example, when the proposed drug product is a combination product that differs from the combination reference listed drug with regard to an active ingredient, and the different active ingredient is an active ingredient of a listed drug. The petitioner shall also include information to show that:

(1) The active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those of the reference listed drug.

(2) The drug product can be expected to have the same therapeutic effect as the reference listed drug when administered to patients for each condition of use in the reference listed drug's labeling for which the applicant seeks approval.

(3) If the proposed drug product is a combination product with one different active ingredient, including a different ester or salt, from the reference listed drug, that the different active ingredient has previously been approved in a listed drug or is a drug that does not meet the definition of "new drug" in section 201(b) of the act.

(e) No later than 90 days after the date a petition that is permitted under paragraph (a) of this section is submitted, FDA will approve or disapprove the petition.

(1) FDA will approve a petition properly submited under this section unless it finds that:

(i) Investigations must be conducted to show the safety and effectiveness of the drug product or of any of its active ingredients, its route of administration, dosage form, or strength which differs from the reference listed drug; or

(ii) For a petition that seeks to change an active ingredient, the drug product that is the subject of the petition is not a combination drug; or

(iii) For a combination drug product that is the subject of the petition and has an active ingredient different from the reference listed drug:

(A) The drug product may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted under § 314.94; or

(B) The petition does not contain information to show that the different active ingredient of the drug product is of the same pharmacological or therapeutic class as the ingredient of the reference listed drug that is to be changed and that the drug product can be expected to have the same therapeutic effect as the reference listed drug when administered to patients for each condition of use in the listed drug's labeling for which the applicant seeks approval; or

(C) The different active ingredient is not an active ingredient in a listed drug or a drug that meets the requirements of section 201(p) of the act; or

(D) The remaining active ingredients are not identical to those of the listed combination drug; or

(iv) Any of the proposed changes from the listed drug would jeopardize the safe or effective use of the product so as to necessitate significant labeling changes to address the newly introduced safety or effectiveness problem; or

(v) FDA has determined that the reference listed drug has been withdrawn from sale for safety or effectiveness reasons under § 314.161, or the reference listed drug has been voluntarily withdrawn from sale and the agency has not determined whether the withdrawal is for safety or effectiveness reasons.

(2) For purposes of this paragraph, "investigations must be conducted" means that information derived from animal or clinical studies is necessary to show that the drug product is safe or effective. Such information may be contained in published or unpublished reports.

(3) If FDA approves a petition submitted under this section, the agency's response may describe what additional information, if any, will be required to support an abbreviated new drug application for the drug product. FDA may, at any time during the course of its review of an abbreviated new drug application, request additional information required to evaluate the change approved under the petition.

(f) FDA may withdraw approval of a petition if the agency receives any information demonstrating that the petition no longer satisfies the conditions under paragraph (e) of this section.

§ 314.94 Content and format of an abbreviated application.

Abbreviated applications are required to be submitted in the form and contain the information required under this section. Two copies of the application are required, an archival copy and a review copy. FDA will maintain guidelines on the format and content of applications to assist applicants in their preparation.

(a) *Abbreviated new drug applications.* Except as provided in paragraph (b) of this section, the applicant shall submit a complete archival copy of the abbreviated new drug application that includes the following:

(1) *Application form.* The applicant shall submit a completed and signed application form that contains the information described under § 314.50(a)(1), (a)(3), (a)(4), and (a)(5). The applicant shall state whether the

submission is an abbreviated application under this section or a supplement to an abbreviated application under § 314.97.

(2) *Table of contents.* the archival copy of the abbreviated new drug application is required to contain a table of contents that shows the volume number and page number of the contents of the submission.

(3) *Basis for abbreviated new drug application submission.* An abbreviated new drug application must refer to a listed drug. Ordinarily, that listed drug will be the drug product selected by the agency as the reference standard for conducting bioequivalence testing. The application shall contain:

(i) The name of the reference listed drug, including its dosage form and strength. For an abbreviated new drug application based on an approverd petition under §10.30 of this chapter or §314.93, the reference listed drug must be the same as the listed drug approved in the petition.

(ii) A statement as to whether, according to the information published in the list, the reference listed drug is entitled to a period of marketing exclusivity under section 505(j)(4)(D) of the act.

(iii) For an abbreviated new drug application based on an approved petition under § 10.30 of this chapter or § 314.93, a reference to FDA-assigned docket number for the petition and a copy of FDA's correspondence approving the petition.

(4) *Conditions of use.* (i) A statement that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the drug product have been previously approved for the reference listed drug.

(ii) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(5) *Active ingredients.* (i) For a single-active-ingredient drug product, information to show that the active ingredient is the same as that of the reference single-active-ingredient listed drug, as follows:

(A) A statement that the active ingredient of the proposed drug product is the same as that of the reference listed drug.

(B) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(ii) For a combination drug product, information to show that the active ingredients are the same as those of the reference listed drug except for any different active ingredient that has been the subject of an approved petition, as follows:

(A) A statement that the active ingredients of the proposed drug product are the same as those of the reference listed drug, or if one of the active ingredients differs from one of the active ingredients of the reference listed drug and the abbreviated application is submitted under the approval of a petition under § 314.93 to vary such active ingredient, information to show that the other active ingredients of the drug product are the same as the other active ingredients of the reference listed drug, information to show that the different active ingredient is an active ingredient of another listed drug or of a drug that does not meet the definition of "new drug" in section 201(p) of the act, and such other information about the different active ingredient that FDA may require.

(B) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(6) *Route of administration, dosage form, and strength.* (i) Information to show that the route of administration, dosage form, and strength of the drug product are the same as those of the reference listed drug except for any differences that have been the subject of an approved petition, as follows:

(A) A statement that the route of administration, dosage form, and strength of the proposed drug product are the same as those of the reference listed drug.

(B) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(ii) If the route of administration, dosage form, or strength of the drug product differs from the reference listed drug and the abbreviated application is submitted under an approved petition under § 314.93, such information about the different route of administration, dosage form, or strength that FDA may require.

(7) *Bioequivalence.* (i) Information that shows that the drug product is bioequivalent to the reference listed drug upon which the applicant relies; or

(ii) If the abbreviated new drug application is submitted under a petition approved under § 314.93, the results of any bioavailability of bioequivalence testing required by the agency, or any other information required by the agency to show that the active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those in the reference listed drug and that the proposed drug product can be expected to have the same therapeutic effect as the reference listed drug. If the proposed drug product contains a different active ingredient than the reference listed drug, FDA will consider the proposed drug product to have the same therapeutic effect as the reference listed drug if the applicant provides information demonstrating that:

(A) There is an adequate scientific basis for determining that substitution of the specific proposed dose of the different active ingredient for the dose of the member of the same pharmacological or therapeutic class in the reference listed drug will yield a resulting drug product whose safety and effectiveness have not been adversely affected.

(B) The unchanged active ingredients in the proposed drug product are bioequivalent to those in the reference listed drug.

(C) The different active ingredient in the proposed drug product is bioequivalent to an approved dosage form containing that ingredient and approved for the same indication as the proposed drug product or is bioequivalent to a drug product offered for that indication which does not meet the definition of "new drug" under section 201(p) of the act.

(iii) For each in vivo bioequivalence study contained in the abbreviated new drug application, a description of the analytical and statistical methods used in each study and a statement with respect to each study that it either was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to the regulations under § 56.104 or § 56.105 of this chapter and that each study was conducted in compliance with the informed consent regulations in part 50 of this chapter.

(8) *Labeling*—(i) *Listed drug labeling.* A copy of the currently approved labeling for the listed drug referred to in the abbreviated new drug application, if the abbreviated new drug application relies on a reference listed drug.

(ii) *Proposed labeling.* Copies of the label and all labeling for the drug product (4 copies of draft labeling or 12 copies of final printed labeling).

(iii) A statement that the applicant's proposed labeling is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section.

(iv) A side-by-side comparison of the applicant's proposed labeling with the

approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label and package insert) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

(9) *Chemistry, manufacturing, and cantrals.* (i) The information required under § 314.50(d)(1).

(ii) *Inactive ingredients.* Unless otherwise stated in paragraphs (a)(9)(iii) through (a)(9)(v) of this section, an applicant shall identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety of the proposed drug product.

(iii) *Inactive ingredient changes permitted in drug products intended for parenteral use.* Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety for the proposed drug product.

(iv) *Inactive ingredient changes permitted in drug products intended far aphthalmic or otic use.* Generally, a drug product intended for ophthalmic or otic use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product, except that, in a product intended for ophthalmic use, an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the listed drug, e.g., by using a balanced salt solution as a diluent as opposed to an isotonic saline solution, or by making a significant change in the pH or other change that may raise questions of irritability.

(v) *Inactive ingredient changes permitted in drug products intended far topical use.* Generally, a drug product intended for topical use shall contain the same inactive ingredients as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product.

(10) *Samples.* The information required under § 314.50(e)(1) and (e)(2)(i). Samples need not be submitted until requested by FDA.

(11) *Other.* The information required under § 314.50(g).

(b) *Drug praducts subject ta the Drug Efficacy Study Implementation (DESI) review.* If the abbreviated new drug application is for a duplicate of a drug product that is subject to FDA's DESI review (a review of drug products approved as safe between 1938 and 1962) or other DESI-like review and the drug product evaluated in the review is a listed drug, the applicant shall comply with the provisions of paragraph (a) of this section.

(c) *Abbreviated antibiatic applicatian.* For applications submitted under section 507 of the act, the applicant shall submit a complete archival copy of the abbreviated application that contains the information described under § 314.50 (a)(1), (a)(3), (a)(4), and (a)(5), (b), (d)(1) and (d)(3), (e), and (g). The applicant shall state whether the submission is an abbreviated application under this section or a supplement to an abbreviated application under § 314.97.

(d) *Farmat af an abbreviated application.* (1) The applicant shall submit a complete archival copy of the abbreviated application as required under paragraphs (a) and (c) of this section. FDA will maintain the archival copy during the review of the application to permit individual reviewers to refer to information that is not contained in their particular technical sections of the application, to give other agency personnel access to the application for official business, and to maintain in one place a complete copy of the application. An applicant may submit all or portions of the archival copy of the abbreviated application in any form (e.g., microfiche, optical disc, and magnetic tape) that the applicant and FDA agree is acceptable.

(2) For abbreviated new drug applications, the applicant shall submit a review copy of the abbreviated application that contains two separate sections. One section shall contain the information described under paragraphs (a)(2) through (a)(6), (a)(8), and (a)(9) of this section 505(j)(2)(A)(vii) of the act and one copy of the analytical methods and descriptive information needed by FDA's laboratories to perform tests on samples of the proposed drug product and to validate the applicant's analytical methods. The other section shall contain the information described under paragraphs (a)(3), (a)(7), and (a)(8) of this section. Each of the sections in the review copy is required to contain a copy of the application form described under § 314.50(a).

(3) For abbreviated antibiotic applications, the applicant shall submit a review copy that contains the technical sections described in § 314.50 (d)(1) and (d)(3). Each of the technical sections in the review copy is required to be separate with a copy of the application form required under § 314.50(a).

(4) The applicant may obtain from FDA sufficient folders to bind the archival and the review copies of the abbreviated application.

§ 314.96 Amendments to an unapproved abbreviated application.

(a) *Abbreviated new drug applicatian.* (1) An applicant may amend an abbreviated new drug application that is submitted under § 314.94, but not yet approved, to revise existing information or provide additional information.

(2) Submission of an amendment containing significant data or information constitutes an agreement between FDA and the applicant to extend the review period only for the time necessary to review the significant data or information and for no more than 180 days.

(3) Submission of an amendment containing significant data or information to resolve deficiencies in the application as set forth in a not approvable letter issued under § 314.120 constitutes an agreement between FDA and the applicant under section

505(j)(4)(A) of the act to extend the date by which the agency is required to reach a decision on the abbreviated new drug application only for the time necessary to review the significant data or information and for no more than 180 days.

(b) *Abbreviated antibiotic application.* The applicant shall comply with the provisions of § 314.60.

§ 314.97 Supplements and other changes to an approved abbreviated application.

The applicant shall comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application.

§ 314.98 Postmarketing reports.

(a) Except as provided in paragraph (b) of this section, each applicant having an approved abbreviated antibiotic application under § 314.94 or approved abbreviated new drug application under § 314.94 that is effective shall comply with the requirements of § 314.80 regarding the reporting and recordkeeping of adverse drug experiences.

(b) Each applicant shall submit one copy of each report required under § 314.80 to the Division of Epidemiology and Surveillance (HFD–730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(c) Each applicant shall make the reports required under § 314.81 and sections 505(k) and 507(g) of the act for each of its approved abbreviated applications.

§ 314.99 Other responsibilities of an applicant of an abbreviated application.

(a) An applicant shall comply with the requirements of § 314.65 regarding withdrawal by the applicant of an unapproved abbreviated application and § 314.72 regarding a change in ownership of an abbreviated application.

(b) An applicant may ask FDA to waive under this section any requirement that applies to the applicant under §§ 314.92 through 314.99. The applicant shall comply with the requirements for a waiver under § 314.90.

23. The heading for subpart D is revised to read as follows:

Subpart D—FDA Action on Applications and Abbreviated Applications

24. Section 314.100 is revised to read as follows:

§ 314.100 Timeframes for reviewing applications and abbreviated applications.

(a) 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, or of an application or abbreviated application for an antibiotic drug under section 507 of the act, FDA will review it and send the applicant either an approval letter under § 314.105, or an approvable letter under § 314.110, or a not approvable letter under § 314.120. This 180-day period is called the "review clock."

(b) During the review period, an applicant may withdraw an application under § 314.65 or an abbreviated application under § 314.99 and later resubmit it. FDA will treat the resubmission as a new application or abbreviated application.

(c) The review clock 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.

25. Section 314.101 is revised to read as follows:

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

(a)(1) Within 60 days after FDA receives an application or abbreviated antibiotic application, the agency will determine whether the application or abbreviated antibiotic application may be filed. The filing of an application or abbreviated antibiotic application means that FDA has made a threshold determination that the application or abbreviated antibiotic application is sufficiently complete to permit a substantive review.

(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for refusing to file the application or abbreviated antibiotic apply, the agency will file the application or abbreviated antibiotic application and notify the applicant in writing. The date of filing will be the date 60 days after the date FDA received the application or abbreviated antibiotic application. The date of filing begins the 180-day period described in section 505(c) of the act. This 180-day period is called the "filing clock."

(3) If FDA refuses to file the application or abbreviated antibiotic application, the agency will notify the applicant in writing and state the reason under paragraph (d) or (e) of this section for the refusal. If FDA refuses to file the application or abbreviated antibiotic application under paragraph (d) of this section, the applicant may request in writing within 30 days of the date of the agency's notification an informal conference with the agency about whether the agency should file the application or abbreviated antibiotic application. If, following the informal conference, the applicant requests that FDA file the application or abbreviated antibiotic application (with or without amendments to correct the deficiencies), the agency will file the application or abbreviated antibiotic application over protest under paragraph (a)(2) of this section, notify the applicant in writing, and review it as filed. If the application or abbreviated antibiotic application is filed over protest, the date of filing will be the date 60 days after the date the applicant requested the informal conference. The applicant need not resubmit a copy of an application or abbreviated antibiotic application that is filed over protest. If FDA refuses to file the application or abbreviated antibiotic application under paragraph (e) of this section, the applicant may amend the application or abbreviated antibiotic application and resubmit it, and the agency will make a determination under this section whether it may be filed.

(b)(1) An abbreviated new drug application will be reviewed after it is submitted to determine whether the abbreviated application may be received. Receipt of an abbreviated new drug application means that FDA has made a threshold determination that the abbreviated application is sufficiently complete to permit a substantive review.

(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for considering the abbreviated new drug application not to have been received applies, the agency will receive the abbreviated new drug application and notify the applicant in writing.

(3) If FDA considers the abbreviated new drug application not to have been received under paragraph (d) or (e) of this section, FDA will notify the applicant, ordinarily by telephone. The applicant may then:

(i) Withdraw the abbreviated new drug application under § 314.99; or

(ii) Amend the abbreviated new drug application to correct the deficiencies; or

(iii) Take no action, in which case FDA will refuse to receive the abbreviated new drug application.

(c) [Reserved]

(d) FDA may refuse to file an application or abbreviated antibiotic application or may not consider an abbreviated new drug application to be received if any of the following applies:

(1) The application or abbreviated application does not contain a completed application form.

(2) The application or abbreviated application is not submitted in the form required under § 314.50 or § 314.94.

(3) The application or abbreviated application is incomplete becasue it does not on its face contain information required under section 505(b), section 505(j), or section 507 of the act and § 314.50 or § 314.94.

(4) The applicant fails to submit a complete environmental assessment, which address each of the items specified in the applicable format under § 25.31 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.24 of this chapter.

(5) The application or abbreviated application does not contain an accurate and complete English translation of each part of the application that is not in English.

(6) The application does not contain a statement for each nonclinical laboratory study that it was conducted in compliance with the requirements set forth in part 58 of this chapter, or, for each study not conducted in compliance with part 58 of this chapter, a brief statement of the reason for the noncompliance.

(7) The application does not contain a statement for each clinical study that it was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to those regulations, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter, or, if the study was subject to but was not conducted in compliance with those regulations, the application does not contain a brief statement of the reason for the noncompliance.

(8) The drug product that is the subject of the submission is already covered by an approved application or abbreviated application and the applicant of the submission:

(i) Has an approved application or abbreviated application for the same drug product; or

(ii) Is merely a distributor and/or repackager of the already approved drug product.

(9) The application is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act.

(e) The agency will refuse to file an application or an abbreviated antibiotic application or will consider an abbreviated new drug application not to have been received if the drug product is subject to licensing by FDA under the Public Health Service Act (42 U.S.C. 201 *et seq.*) and subchapter F of this chapter.

(f)(1) Within 180 days after the date of filing, plus the period of time the review period was extended (if any), FDA will either:

(i) Approve the application or abbreviated antibiotic application; or

(ii) Issue a notice of opportunity for hearing if the applicant asked FDA to provide it an opportunity for a hearing on an application or abbreviated antibiotic application in response to an approvable letter or a not approvable letter.

(2) Within 180 days after the date of receipt, plus the period of time the review clock was extended (if any), FDA will either approve or disapprove the abbreviated new drug application. 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 not approvable letter.

(3) This paragraph does not apply to applications or abbreviated applications that have been withdrawn from FDA review by the applicant.

26. Section 314.102 is revised to read as follows:

§ 314.102 Communications between FDA and applicants.

(a) *General principles.* During the course of reviewing an application or an abbreviated application, FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process. Such communication may take the form of telephone conversations, letters, or meetings, whichever is most appropriate to discuss the particular issue at hand. Communications shall be appropriately documented in the application in accordance with § 10.65 of this chapter. Further details on the procedures for communication between FDA and applicants are contained in a staff manual guide that is publicly available.

(b) *Notification of easily correctable deficiencies.* 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 chemistry, manufacturing, and controls issues. The agency will also inform applicants promptly of its need for more data or information or for technical changes in the application or the abbreviated application needed to facilitate the agency review. This early communication is intended to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed. Such early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application or abbreviated application by agency managers as well as reviewing staff. Instead, major scientific issues will ordinarily be addressed in an action letter.

(c) *Ninety-day conference.* Approximately 90 days after the agency receives the application, FDA will provide applicants with an opportunity to meet with agency reviewing officials. The purpose of the meeting will be to inform applicants of the general progress and status of their applications, and to advise applicants of deficiencies that have been identified by that time and that have not already been communicated. This meeting will be available on applications for all new chemical entities and major new indications of marketed drugs. Such meetings will be held at the applicant's option, and may be held by telephone if mutually agreed upon. Such meetings would not ordinarily be held on abbreviated applications because they are not submitted for new chemical entities or new indications.

(d) *End of review conference.* At the conclusion of FDA's review of an application or an abbreviated application as designated by the issuance of an approvable or not approvable letter, FDA 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. 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 shall be directed to the director of the division responsible for reviewing the application or abbreviated application.

(e) *Other meetings.* Other meetings between FDA and applicants may be held, with advance notice, to discuss scientific, medical, and other issues that arise during the review process. Requests for meetings shall be directed to the director of the division

responsible for reviewing the application or abbreviated application. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times. However, "drop-in" visits (i.e., an unannounced and unscheduled visit by a company representative) are discouraged except for urgent matters, such as to discuss an important new safety issue.

27. Section 314.103 is amended by revising paragraph (a), the first sentence in paragraph (b), and the fourth sentence in paragraph (c)(2) to read as follows:

§ 314.103 Dispute resolution.

(a) *General.* FDA is committed to resolving differences between applicants and FDA reviewing divisions with respect to technical requirements for applications or abbreviated applications as quickly and amicably as possible through the cooperative exchange of information and views.

(b) *Administrative and procedural issues.* When administrative or procedural disputes arise, the applicant should first attempt to resolve the matter with the division responsible for reviewing the application or abbreviated application, beginning with the consumer safety officer assigned to the application or abbreviated application.

* * *

(c) * * *

(2) * * * Requests for such meetings shall be directed to the director of the division responsible for reviewing the application or abbreviated application.

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28. Section 314.104 is revised to read as follows:

§ 314.104 Drugs with potential for abuse.

The Food and Drug Administration will inform the Drug Enforcement Administration under section 201(f) of the Controlled Substances Act (21 U.S.C. 801) when an application or abbreviated application is submitted for a drug that appears to have an abuse potential.

29. Section 314.105 is revised to read as follows:

§ 314.105 Approval of an application and an abbreviated application.

(a) The Food and Drug Administration will approve an application or an abbreviated antibiotic application and sent the applicant an approval letter if none of the reasons in § 314.125 for refusing to approve the application or abbreviated antibiotic application applies. An approval becomes effective on the date of the issuance of the approval letter, except with regard to an approval under section 505(b)(2) of the act with a delayed effective date. An approval with a delayed effective date is tentative and does not become final until the effective date. When FDA sends an applicant an approval letter for an antibiotic, it will promulgate a regulation under § 314.300 providing for certification of the drug, if necessary. A new drug product or antibiotic approved under this paragraph may not be marketed until an approval is effective. Marketing of an antibiotic need not await the promulgation of a regulation under § 314.300.

(b) FDA will approve an application or abbreviated antibiotic application and issue the applicant an approval letter (rather than an approvable letter under § 314.110) on the basis of draft labeling if the only deficiencies in the application or abbreviated antibiotic application concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.

(c) FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling, and an abbreviated application after it determines that the drug meets the statutory standards for manufacturing and controls, labeling, and, where applicable, bioequivalence. While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards. FDA makes its views on drug products and classes of drugs available through guidelines, recommendations, and other statements of policy.

(d) FDA will approve an abbreviated new drug application and send the applicant an approval letter if none of the reasons in § 314.127 for refusing to approve the abbreviated new drug application applies. The approval becomes effective on the date of the issuance of the agency's approval letter unless the approval letter provides for a delayed effective date. An approval with a delayed effective date is tentative and does not become final until the effective date. A new drug product approved under this paragraph may not be introduced or delivered for introduction into interstate commerce until approval of the abbreviated new drug application is effective. Ordinarily, the effective date of approval will be stated in the approval letter.

30. Section 314.110 is revised to read as follows:

§ 314.110 Approvable letter to the applicant.

(a) In selected circumstances, it is useful at the end of the review period for the Food and Drug Administration to indicate to the applicant that the application or abbreviated application is basically approvable providing certain issues are resolved. An approvable letter may be issued in such circumstances. FDA will send the applicant an approvable letter if the application or abbreviated application substantially meets the requirements of this part and the agency believes that it can approve the application or abbreviated application if specific additional information or material is submitted or specific conditions (for example, certain changes in labeling) are agreed to by the applicant. The approvable letter will describe the information or material FDA requires or the conditions the applicant is asked to meet. As a practical matter, the approvable letter will serve in most instances as a mechanism for resolving outstanding issues on drugs that are about to be approved and marketed. For an application or an abbreviated antibiotic application, the applicant shall, within 10 days after the date of the approvable letter:

(1) Amend the application or abbreviated antibiotic application or notify FDA of an intent to file an amendment. The filing of an amendment or notice of intent to file an amendment constitutes an agreement by the applicant to extend the review period for 45 days after the date FDA receives the amendment. The extension is to permit the agency to review the amendment;

(2) Withdraw the application or abbreviated antibiotic application. FDA will consider the applicant's failure to respond within 10 days to an approvable letter to be a request by the applicant to withdraw the application under § 314.65 or the abbreviated antibiotic application under § 314.99. A decision to withdraw an application or abbreviated antibiotic application is without prejudice to a refiling;

(3) For a new drug application or abbreviated antibiotic application, 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 under section 505(d) of the act. The applicant shall submit the request to the Division of Regulatory Affairs (HFD–360), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Within 60 days of the date of the approvable letter, or within a different time period to which FDA and the applicant agree, the agency will either approve the application or abbreviated antibiotic application under § 314.105 or refuse to approve the application or abbreviated antibiotic application under § 314.125 and give the applicant written notice of an opportunity for a hearing under § 314.200 and section 505(c)(2) of the act on the question of whether there are grounds for denying approval of the application under section 505(d) of the act;

(4) For an antibiotic, file a petition or notify FDA of an intent to file a petition proposing the issuance, amendment, or repeal of a regulation under § 314.300 and section 507(f) of the act; or

(5) Notify FDA that the applicant agrees to an extension of the review period under section 505(c) of the act, so that the applicant can determine whether to respond further under paragraph (a)(1), (a)(2), (a)(3), or (a)(4) of this section. The applicant's notice is required to state the length of the extension. FDA will honor any reasonable request for such an extension. FDA will consider the applicant's failure to respond further within the extended review period to be a request to withdraw the application under § 314.65 or the abbreviated antibiotic application under § 314.99. A decision to withdraw an application or abbreviated antibiotic application is without prejudice to a refiling.

(b) FDA will send the applicant of an abbreviated new drug application an approvable letter only if the application substantially meets the requirements of this part and the agency believes that it can approve the abbreviated application if minor deficiencies (e.g., labeling deficiencies) are corrected. The approvable letter will describe the deficiencies and state a time period within which the applicant must respond. Unless the applicant corrects the deficiencies by amendment within the specified time period, FDA will refuse to approve the abbreviated application under § 314.127. Within 10 days after the date of the approvable letter, the applicant may also 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 abbreviated new drug application. Applicants who request a hearing shall submit the request to the Division of Regulatory Affairs (HFD–360), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

31. Section 314.120 is revised to read as follows:

§ 314.120 Not approvable letter to the applicant.

(a) The Food and Drug Administration will send the applicant a not approvable letter if the agency believes that the application or abbreviated antibiotic application may not be approved for one of the reasons given in § 314.125 or the abbreviated new drug application may not be approved for one of the reasons given in § 314.127. The not approvable letter will describe the deficiencies in the application or abbreviated application. Except as provided in paragraph (b) of this section, within 10 days after the date of the not approvable letter, the applicant shall:

(1) Amend the application or abbreviated application or notify FDA of an intent to file an amendment. The filing of an amendment or a notice of intent to file an amendment constitutes an agreement by the applicant to extend the review period under § 314.60 or § 314.96;

(2) Withdraw the application or abbreviated application. Except as provided in paragraph (b) of this section, FDA will consider the applicant's failure to respond within 10 days to a not approvable letter to be a request by the applicant to withdraw the application under § 314.65 or abbreviated application under § 314.99. A decision to withdraw the application or abbreviated application is without prejudice to refiling;

(3) For a new drug application or an abbreviated application, 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 under section 505(d) or (j)(3) of the act. The applicant shall submit the request to the Division of Regulatory Affairs (HFD–360), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Within 60 days of the date of the not approvable letter, 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 or abbreviated antibiotic application under § 314.125 or abbreviated new drug 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)(4)(C) of the act on the question of whether there are grounds for denying approval of the application under section 505(d) or (j)(3) of the act;

(4) For an antibiotic application, file a petition or notify FDA of an intent to file a petition proposing the issuance, amendment, or repeal of a regulation under § 314.300 and section 507(f) of the act; or

(5) Notify FDA that the applicant agrees to an extension of the review period under section 505(c)(1) or (j)(4)(A) of the act, so that the applicant can determine whether to respond further under paragraph (a)(1), (a)(2), (a)(3), or (a)(4) of this section. The applicant's notice is required to state the length of the extension. FDA will honor any reasonable request for such an extension. FDA will consider the applicant's failure to respond further within the extended review period to be a request to withdraw the application under § 314.65 or abbreviated application under § 314.99. A decision to withdraw an application or abbreviated application is without prejudice to a refiling.

(b) With the exception of a request for an opportunity for a hearing under paragraph (a)(3) of this section, the 10-day time period in this section for responding to a not approvable letter does not apply to abbreviated new drug applications. FDA may consider the applicant's failure to respond within 180 days to a not approvable letter to be a request by the applicant to withdraw the abbreviated new drug application under § 314.99.

32. New § 314.122 is added to subpart D to read as follows:

§ 314.122 Submitting an abbreviated application for, or a 505(j)(2)(C) petition that relies on, a listed drug that is no longer marketed.

(a) An abbreviated new drug application that refers to, or a petition under section 505(j)(2)(C) of the act and § 314.93 that relies on, a listed drug that has been voluntarily withdrawn from sale in the United States must be accompanied by a petition seeking a determination whether the listed drug was withdrawn for safety or effectiveness reasons. The petition must be submitted under §§ 10.25(a) and 10.30 of this chapter and must contain all evidence available to the petitioner concerning the reasons for the withdrawal from sale.

(b) When a petition described in paragraph (a) of this section is submitted, the agency will consider the evidence in the petition and any other evidence before the agency, and determine whether the listed drug is withdrawn from sale for safety or effectiveness reasons, in accordance with procedures in § 314.161.

(c) An abbreviated new drug application described in paragraph (a) of this section will be disapproved, under § 314.127(a)(11), and a 505(j)(2)(C) petition described in paragraph (a) of this section will be disapproved, under § 314.93(e)(1)(iv), unless the agency determines that the withdrawal of the listed drug was not for safety or effectiveness reasons.

(d) Certain drug products approved for safety and effectiveness that were no longer marketed on September 24, 1984, are not included in the list. Any person who wishes to obtain marketing approval for such a drug product under an abbreviated new drug application must petition FDA for a determination whether the drug product was withdrawn from the market for safety or effectiveness reasons and request that the list be amended to include the drug product. A person seeking such a determination shall use the petition procedures established in § 10.30 of this chapter. The petitioner shall include in the petition information to show that the drug product was approved for safety and effectiveness and all evidence available to the petitioner concerning the reason that marketing of the drug product ceased.

33. Section 314.125 is amended by revising the section heading, the introductory text of paragraph (a), the introductory text of paragraph (b), paragraphs (b)(7), (b)(9), (b)(10), (b)(12), (b)(14), (b)(15), (b)(16), and (b)(17), and by adding new paragraph (b)(18) to read as follows:

§ 314.125 Refusal to approve an application or abbreviated antibiotic application.

(a) The Food and Drug Administration will refuse to approve the application or abbreviated antibiotic application and for a new drug give the applicant written notice of an opportunity for a hearing under § 314.200 on the question of whether there are grounds for denying approval of the application under section 505(d) of the act, or for an antibiotic publish a proposed regulation based on an acceptable petition under § 314.300, if:

* * * * *

(b) FDA may refuse to approve an application or abbreviated antibiotic application for any of the following reasons:

* * * * *

(7) The application or abbreviated antibiotic application contains an untrue statement of a material fact.

* * * * *

(9) The application or abbreviated antibiotic application does not contain bioavailability or bioequivalence data required under part 320 of this chapter.

(10) A reason given in a letter refusing to file the application or abbreviated antibiotic application under § 314.101(d), if the deficiency is not corrected.

* * * * *

(12) The applicant does not permit a properly authorized officer or employee of the Department of Health and Human Services an adequate opportunity to inspect the facilities, controls, and any records relevant to the application or abbreviated antibiotic application.

* * * * *

(14) The application or abbreviated antibiotic application does not contain an explanation of the omission of a report of any investigation of the drug product sponsored by the applicant, or an explanation of the omission of other information about the drug pertinent to an evaluation of the application or abbreviated antibiotic application that is received or otherwise obtained by the applicant from any source.

(15) A nonclinical laboratory study that is described in the application or abbreviated antibiotic application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling was not conducted in compliance with the good laboratory practice regulations in part 58 of this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

(16) Any clinical investigation involving human subjects described in the application or abbreviated antibiotic application, subject to the institutional review board regulations in part 58 of this chapter or informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected.

(17) The applicant or contract research organization that conducted a bioavailability or bioequivalence study contained in the application or abbreviated antibiotic application refuses to permit an inspection of facilities or records relevant to the study by a properly authorized officer or employee of the Department of Health and Human Services or refuses to submit reserve samples of the drug products used in the study when requested by FDA.

(18) For a new drug, the application failed to contain the patent information required by section 505(b)(1) of the act.

* * * * *

34. New § 314.127 is added to subpart D to read as follows:

§ 314.127 Refusal to approve an abbreviated new drug application

(a) FDA will refuse to approve an abbreviated application for a new drug under section 505(j) of the act for any of the following reasons:

(1) The methods used in or the facilities and controls used for the manufacture, processing, and packing of the drug product are inadequate to ensure and preserve its identity, strength, quality, and purity.

(2) Information submitted with the abbreviated new drug application is insufficient to show that each of the proposed conditions of use has been previously approved for the listed drug referred to in the application.

(3)(i) If the reference listed drug has only one active ingredient, information submitted with the abbreviated new drug application is insufficient to show that the active ingredient is the same as that of the reference listed drug;

(ii) If the reference listed drug has more than one active ingredient, information submitted with the abbreviated new drug application is insufficient to show that the active ingredients are the same as the active ingredients of the reference listed drug; or

(iii) If the reference listed drug has more than one active ingredient and if the abbreviated new drug application is for a drug product that has an active ingredient different from the reference listed drug:

(A) Information submitted with the abbreviated new drug application is insufficient to show:

(*1*) That the other active ingredient are the same as the active ingredients of the reference listed drug; or

(*2*) That the different active ingredient is an active ingredient of a listed drug or a drug that does not meet the requirements of section 201(p) of the act; or

(b) No petition to submit an abbreviated application for the drug product with the different active ingredient was approved under § 314.93.

(4)(i) If the abbreviated new drug application is for a drug product whose

route of administration, dosage form, or strength purports to be the same as that of the listed drug referred to in the abbreviated new drug application, information submitted in the abbreviated new drug application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the reference listed drug; or

(ii) If the abbreviated new drug application is for a drug product whose route of administration, dosage form, or strength is different from that of the listed drug referred to in the application, no petition to submit an abbreviated new drug application for the drug product with the different route of administration, dosage form, or strength was approved under § 314.93.

(5) If the abbreviated new drug application was submitted under the approval of a petition under § 314.93, the abbreviated new drug application did not contain the information required by FDA with respect to the active ingredient, route of administration, dosage form, or strength that is not the same as that of the reference listed drug.

(6)(i) Information submitted in the abbreviated new drug application is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the abbreviated new drug application; or

(ii) If the abbreviated new drug application was submitted under a petition approved under § 314.93, information submitted in the abbreviated new drug application is insufficient to show that the active ingredients of the drug product are of the same pharmacological or therapeutic class as those of the reference listed drug and that the drug product can be expected to have the same therapeutic effect as the reference listed drug when administered to patients for each condition of use approved for the reference listed drug.

(7) Information submitted in the abbreviated new drug application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the abbreviated new drug application except for changes required because of differences approved in a petition under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers or because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use.

(8)(i) Information submitted in the abbreviated new drug application of any other information available to FDA shows that:

(A) The inactive ingredients of the drug product are unsafe for use, as described in paragraph (a)(8)(ii) of this section, under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug product; or

(B) The composition of the drug product is unsafe, as described in paragraph (a)(8)(ii) of this section, under the conditions prescribed, recommended, or suggested in the proposed labeling because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.

(ii)(A) FDA will consider the inactive ingredients or composition of a drug product unsafe and refuse to approve an abbreviated new drug application under paragraph (a)(8)(i) of this section if, on the basis of information available to the agency, there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety. From its experience with reviewing inactive ingredients, and from other information available to it, FDA may identify changes in inactive ingredients or composition that may adversely affect a drug product's safety. The inactive ingredients or composition of a proposed drug product will be considered to raise serious questions of safety if the product incorporates one or more of these changes. Examples of the changes that may raise serious questions of safety include, but are not limited to, the following:

(*1*) A change in an inactive ingredient so that the product does not comply with an official compendium.

(*2*) A change in composition to include an inactive ingredient that has not been previously approved in a drug product for human use by the same route of administration.

(*3*) A change in the composition of a parenteral drug product to include an inactive ingredient that has not been previously approved in a parenteral drug product.

(*4*) A change in composition of a drug product for ophthalmic use to include an inactive ingredient that has not been previously approved in a drug for ophthalmic use.

(*5*) The use of a delivery or a modified release mechanism never before approved for the drug.

(*6*) A change in composition to include a significantly greater content of one or more inactive ingredients than previously used in the drug product.

(*7*) If the drug product is intended for topical administration, a change in the properties of the vehicle or base that might increase absorption of certain potentially toxic active ingredients thereby affecting the safety of the drug product, or a change in the lipophilic properties of a vehicle or base, e.g., a change from an oleaginous to a water soluble vehicle or base.

(B) FDA will consider an inactive ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the abbreviated new drug application unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and, if it differs from the listed drug in a preservative, buffer, or antioxidant, the application contains sufficient information to demonstrate that the difference does not affect the safety of the drug product.

(C) FDA will consider an inactive ingredient in, or the composition of, a drug product intended for ophthalmic or otic use unsafe and will refuse to approve the abbreviated new drug application unless it contains the same inactive ingredients, other than preservatives, buffers, substances to adjust tonicity, or thickening agents, in the same concentration as the listed drug, and if it differs from the listed drug in a preservative, buffer, substance to adjust tonicity, or thickening agent, the application contains sufficient information to demonstrate that the difference does not affect the safety of the drug product and the labeling does not claim any therapeutic advantage over or difference from the listed drug.

(9) Approval of the listed drug referred to in the abbreviated new drug application has been withdrawn or suspended for grounds described in § 314.150(a) or FDA has published a notice of opportunity for hearing to withdraw approval of the reference listed drug under § 314.150(a).

(10) Approval of the listed drug referred to in the abbreviated new drug application has been withdrawn under § 314.151 or FDA has proposed to withdraw approval of the reference listed drug under § 314.151(a).

(11) FDA has determined that the reference listed drug has been withdrawn from sale for safety or effectiveness reasons under § 314.161, or the reference listed drug has been voluntarily withdrawn from sale and the agency has not determined whether the withdrawal is for safety or effectiveness reasons, or approval of the reference listed drug has been suspended under

§ 314.153, or the agency has issued an initial decision proposing to suspend the reference listed drug under § 314.153(a)(1).

(12) The abbreviated new drug application does not meet any other requirement under section 505(j)(2)(A) of the act.

(13) The abbreviated new drug application contains an untrue statement of material fact.

(b) FDA may refuse to approve an abbreviated application for a new drug if the applicant or contract research organization that conducted a bioavailability or bioequivalence study contained in the abbreviated new drug application refuses to permit an inspection of facilities or records relevant to the study by a properly authorized officer or employee of the Department of Health and Human Services or refuses to submit reserve samples of the drug products used in the study when requested by FDA.

35. Section 314.150 is revised to read as follows:

§ 314.150 Withdrawal of approval of an application or abbreviated application.

(a) The Food and Drug Administration will notify the applicant, and, if appropriate, all other persons who manufacture or distribute identical, related, or similar drug products as defined in §§ 310.6 and 314.151(a) of this chapter and for a new drug afford an opportunity for a hearing on a proposal to withdraw approval of the application or abbreviated new drug application under section 505(e) of the act and under the procedure in § 314.200, or, for an antibiotic, rescind a certification or release, or amend or repeal a regulation providing for certification under section 507 of the act and under the procedure in § 314.300, if any of the following apply:

(1) The Secretary of Health and Human Services has suspended the approval of the application or abbreviated application for a new drug on a finding that there is an imminent hazard to the public health. FDA will promptly afford the applicant an expedited hearing following summary suspension on a finding of imminent hazard to health.

(2) FDA finds:

(i) That clinical or other experience, tests, or other scientific data show that the drug is unsafe for use under the conditions of use upon the basis of which the application or abbreviated application was approved; or

(ii) That new evidence of clinical experience, not contained in the application or not available to FDA until after the application or abbreviated application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application or abbreviated application was approved, evaluated together with the evidence available when the application or abbreviated application was approved, reveal that the drug is not shown to be safe for use under the conditions of use upon the basis of which the application or abbreviated application was approved; or

(iii) Upon the basis of new information before FDA with respect to the drug, evaluated together with the evidence available when the application or abbreviated application was approved, that there is a lack of substantial evidence from adequate and well-controlled investigations as defined in § 314.126, that the drug will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in its labeling; or

(iv) That the application or abbreviated application contains any untrue statement of a material fact; or

(v) That the patent information prescribed by section 505(c) of the act was not submitted within 30 days after the receipt of written notice from FDA specifying the failure to submit such information; or

(b) FDA may notify the applicant, and, if appropriate, all other persons who manufacture or distribute identical, related, or similar drug products as defined in § 310.6, and for a new drug afford an opportunity for a hearing on a proposal to withdraw approval of the application or abbreviated new drug application under section 505(e) of the act and under the procedure in § 314.200, or, for an antibiotic, rescind a certification or release, or amend or repeal a regulation providing for certification under section 507 of the act and the procedure in § 314.300, if the agency finds:

(1) That the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain required records or to make required reports under section 505(k) or 507(g) of the act and § 314.80, § 314.81, or § 314.98, or that the applicant has refused to permit access to, or copying or verification of, its records.

(2) That on the basis of new information before FDA, evaluated together with the evidence available when the application or abbreviated application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to ensure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the agency.

(3) That on the basis of new information before FDA, evaluated together with the evidence available when the application or abbreviated application was approved, the labeling of the drug, based on a fair evaluation of all material facts, is false or misleading in any particular, and the labeling was not corrected by the applicant within a reasonable time after receipt of written notice from the agency.

(4) That the applicant has failed to comply with the notice requirements of section 510(j)(2) of the act.

(5) That the applicant has failed to submit bioavailability or bioequivalence data required under part 320 of this chapter.

(6) The application or abbreviated application does not contain an explanation of the omission of a report of any investigation of the drug product sponsored by the applicant, or an explanation of the omission of other information about the drug pertinent to an evaluation of the application or abbreviated application that is received or otherwise obtained by the applicant from any source.

(7) That any nonclinical laboratory study that is described in the application or abbreviated application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its labeling was not conducted in compliance with the good laboratory practice regulations in part 58 of this chapter and no reason for the noncompliance was provided or, if it was, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

(8) Any clinical investigation involving human subjects described in the application or abbreviated application, subject to the institutional review board regulations in part 56 of this chapter or informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected.

(9) That the applicant or contract research organization that conducted a bioavailability or bioequivalence study contained in the application or abbreviated application refuses to permit an inspection of facilities or records relevant to the study by a properly authorized officer or employee

of the Department of Health and Human Services or refuses to submit reserve samples of the drug products used in the study when requested by FDA.

(10) That the labeling for the drug product that is the subject of the abbreviated new drug application is no longer consistent with that for the listed drug referred to in the abbreviated new drug application, except for differences approved in the abbreviated new drug application or those differences resulting from:

(i) A patent on the listed drug issued after approval of the abbreviated new drug application; or

(ii) Exclusivity accorded to the listed drug after approval of the abbreviated new drug application that do not render the drug product less safe or effective than the listed drug for any remaining, nonprotected condition(s) of use.

(c) FDA will withdraw approval of an application or abbreviated application if the applicant requests its withdrawal because the drug subject to the application or abbreviated application is no longer being marketed, provided none of the conditions listed in paragraphs (a) and (b) of this section applies to the drug. FDA will consider a written request for a withdrawal under this paragraph to be a waiver of an opportunity for hearing otherwise provided for in this section. Withdrawal of approval of an application or abbreviated application under this paragraph is without prejudice to refiling.

(d) FDA may notify an applicant that it believes a potential problem associated with a drug is sufficiently serious that the drug should be removed from the market and may ask the applicant to waive the opportunity for hearing otherwise provided for under this section, to permit FDA to withdraw approval of the application or abbreviated application for the product, and to remove voluntarily the product from the market. If the applicant agrees, the agency will not make a finding under paragraph (b) of this section, but will withdraw approval of the application or abbreviated application in a notice published in the **Federal Register** that contains a brief summary of the agency's and the applicant's views of the reasons for withdrawal.

36. New § 314.151 is added to subpart D to read as follows:

§ 314.151 Withdrawal of approval of an abbreviated new drug application under section 505(j)(5) of the act.

(a) Approval of an abbreviated new drug application approved under § 314.105(d) may be withdrawn when the agency withdraws approval, under § 314.150(a) or under this section, of the approved drug referred to in the abbreviated new drug application. If the agency proposed to withdraw approval of a listed drug under § 314.150(a), the holder of an approved application for the listed drug has a right to notice and opportunity for hearing. The published notice of opportunity for hearing will identify all drug products approved under § 314.105(d) whose applications are subject to withdrawal under this section if the listed drug is withdrawn, and will propose to withdraw such drugs. Holders of approved applications for the identified drug products will be provided notice and an opportunity to respond to the proposed withdrawal of their applications as described in paragraphs (b) and (c) of this section.

(b)(1) The published notice of opportunity for hearing on the withdrawal of the listed drug will serve as notice to holders of identified abbreviated new drug applications of the grounds for the proposed withdrawal.

(2) Holders of applications for drug products identified in the notice of opportunity for hearing may submit written comments on the notice of opportunity for hearing issued on the proposed withdrawal of the listed drug. If an abbreviated new drug application holder submits comments on the notice of opportunity for hearing and a hearing is granted, the abbreviated new drug application holder may participate in the hearing as a nonparty participant as provided for in § 12.89 of this chapter.

(3) Except as provided in paragraphs (c) and (d) of this section, the approval of an abbreviated new drug application for a drug product identified in the notice of opportunity for hearing on the withdrawal of a listed drug will be withdrawn when the agency has completed the withdrawal of approval of the listed drug.

(c)(1) If the holder of an application for a drug identified in the notice of opportunity for hearing has submitted timely comments but does not have an opportunity to participate in a hearing because a hearing is not requested or is settled, the submitted comments will be considered by the agency, which will issue an initial decision. The initial decision will respond to the comments, and contain the agency's decision whether there are grounds to withdraw approval of the listed drug and of the abbreviated new drug applications on which timely comments were submitted. The initial decision will be sent to each abbreviated new drug application holder that has submitted comments.

(2) Abbreviated new drug application holders to whom the initial decision was sent may, within 30 days of the issuance of the initial decision, submit written objections.

(3) The agency may, at its discretion, hold a limited oral hearing to resolve dispositive factual issues that cannot be resolved on the basis of written submissions.

(4) If there are no timely objections to the initial decision, it will become final at the expiration of 30 days.

(5) If timely objections are submitted, they will be reviewed and responded to in a final decision.

(6) The written comments received, the initial decision, the evidence relied on in the comments and in the initial decision, the objections to the initial decision, and, if a limited oral hearing has been held, the transcript of that hearing and any documents submitted therein, shall form the record upon which the agency shall make a final decision.

(7) Except as provided in paragraph (d) of this section, any abbreviated new drug application whose holder submitted comments on the notice of opportunity for hearing shall be withdrawn upon the issuance of a final decision concluding that the listed drug should be withdrawn for grounds as described in § 314.150(a). The final decision shall be in writing and shall constitute final agency action, reviewable in a judicial proceeding.

(8) Documents in the record will be publicly available in accordance with § 10.20(j) of this chapter. Documents available for examination or copying will be placed on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration, room. 1–23, 12420 Parklawn Dr., Rockville, MD 20857, promptly upon receipt in that office.

(d) If the agency determines, based upon information submitted by the holder of an abbreviated new drug application, that the grounds for withdrawal of the listed drug are not applicable to a drug identified in the notice of opportunity for hearing, the final decision will state that the approval of the abbreviated new drug application for such drug is not withdrawn.

37. Section 314.152 is revised to read as follows:

§ 314.152 Notice of withdrawal of approval of an application or abbreviated application for a new drug.

If the Food and Drug Administration withdraws approval of an application or abbreviated application for a new drug, FDA will publish a notice in the **Federal Register** announcing the withdrawal of

approval. If the application or abbreviated application was withdrawn for grounds described in § 314.150(a) or § 314.151, the notice will announce the removal of the drug from the list of approved drugs published under section 505(j)(6) of the act and shall satisfy the requirement of § 314.162(b).

38. New § 314.153 is added to Subpart D to read as follows:

§ 314.153 Suspension of approval of an abbreviated new drug application.

(a) *Suspension of approval.* The approval of an abbreviated new drug application approved under § 314.105(d) shall be suspended for the period stated when:

(1) The Secretary of the Department of Health and Human Services, under the imminent hazard authority of section 505(e) of the act or the authority of this paragraph, suspends approval of a listed drug referred to in the abbreviated new drug application, for the period of the suspension;

(2) The agency, in the notice described in paragraph (b) of this section, or in any subsequent written notice given an abbreviated new drug application holder by the agency, concludes that the risk of continued marketing and use of the drug is inappropriate, pending completion of proceedings to withdraw or suspend approval under § 314.151 or paragraph (b) of this section; or

(3) The agency, under the procedures set forth in paragraph (b) of this section, issues a final decision stating the determination that the abbreviated application is suspended because the listed drug on which the approval of the abbreviated new drug application depends has been withdrawn from sale for reasons of safety or effectiveness or has been suspended under paragraph (b) of this section. The suspension will take effect on the date stated in the decision and will remain in effect until the agency determines that the marketing of the drug has resumed or that the withdrawal is not for safety or effectiveness reasons.

(b) *Procedures for suspension of abbreviated new drug applications when a listed drug is voluntarily withdrawn for safety or effectiveness reasons.* (1) If a listed drug is voluntarily withdrawn from sale, and the agency determines that the withdrawal from sale was for reasons of safety or effectiveness, the agency will send each holder of an approved abbreviated new drug application that is subject to suspension as a result of this determination a copy of the agency's initial decision setting forth the reasons for the determination. The initial decision will also be placed on file with the Dockets Management Branch (HFA–305), Food and Drug Administration, room 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

(2) Each abbreviated new drug application holder will have 30 days from the issuance of the initial decision to present, in writing, comments and information bearing on the initial decision. If no comments or information is received, the initial decision will become final at the expiration of 30 days.

(3) Comments and information received within 30 days of the issuance of the initial decision will be considered by the agency and responded to in a final decision.

(4) The agency may, in its discretion, hold a limited oral hearing to resolve dispositive factual issues that cannot be resolved on the basis of written submissions.

(5) If the final decision affirms the agency's initial decision that the listed drug was withdrawn for reasons of safety or effectiveness, the decision will be published in the **Federal Register** in compliance with § 314.152, and will, except as provided in paragraph (b)(6) of this section, suspend approval of all abbreviated new drug applications identified under paragraph (b)(1) of this section and remove from the list the listed drug and any drug whose approval was suspended under this paragraph. The notice will satisfy the requirement of § 314.162(b). The agency's final decision and copies of materials on which it relies will also be filed with the Dockets Management Branch (address in paragraph (b)(1) of this section).

(6) If the agency determines in its final decision that the listed drug was withdrawn for reasons of safety or effectiveness but, based upon information submitted by the holder of an abbreviated new drug application, also determines that the reasons for the withdrawal of the listed drug are not relevant to the safety and effectiveness of the drug subject to such abbreviated new drug application, the final decision will state that the approval of such abbreviated new drug application is not suspended.

(7) Documents in the record will be publicly available in accordance with § 10.20(j) of this chapter. Documents available for examination or copying will be placed on public display in the Dockets Management Branch (address in paragraph (b)(1) of this section) promptly upon receipt in that office.

39. Section 314.160 is revised to read as follows:

§ 314.160 Approval of an application or abbreviated application for which approval was previously refused, suspended, or withdrawn.

Upon the Food and Drug Administration's own initiative or upon request of an applicant, FDA may, on the basis of new data, approve an application or abbreviated application which it had previously refused, suspended, or withdrawn approval. FDA will publish a notice in the **Federal Register** annqunc ing the approval.

40. New §§ 314.161 and 314.162 are added to subpart D to read as follows:

§ 314.161 Determination of reasons for voluntary withdrawal of a listed drug.

(a) A determination whether a listed drug that has been voluntarily withdrawn from sale was withdrawn for safety or effectiveness reasons may be made by the agency at any time after the drug has been voluntarily withdrawn from sale, but must be made:

(1) Prior to approving an abbreviated new drug application that refers to the listed drug;

(2) Whenever a listed drug is voluntarily withdrawn from sale and abbreviated new drug applications that referred to the listed drug have been approved; and

(3) When a person petitions for such a determination under §§ 10.25(a) and 10.30 of this chapter.

(b) Any person may petition under §§ 10.25(a) and 10.30 of this chapter for a determination whether a listed drug has been voluntarily withdrawn for safety or effectiveness reasons. Any such petition must contain all evidence available to the petitioner concerning the reason that the drug is withdrawn from sale.

(c) If the agency determines that a listed drug is withdrawn from sale for safety or effectiveness reasons, the agency will, except as provided in paragraph (d) of this section, publish a notice of the determination in the **Federal Register**.

(d) If the agency determines under paragraph (a) of this section that a listed drug is withdrawn from sale for safety and effectiveness reasons and there are approved abbreviated new drug applications that are subject to suspension under section 505(j)(5) of the act, FDA will initiate a proceeding in accordance with § 314.153(b).

(e) A drug that the agency determines is withdrawn for safety or effectiveness reasons will be removed from the list, under § 314.162. The drug may be relisted if the agency has evidence that marketing of the drug has resumed or that the withdrawal is not for safety or

effectiveness reasons. A determination that the drug is not withdrawn for safety or effectiveness reasons may be made at any time after its removal from the list, upon the agency's initiative, or upon the submission of a petition under §§ 10.25(a) and 10.30 of this chapter. If the agency determines that the drug is not withdrawn for safety or effectiveness reasons, the agency shall publish a notice of this determination in the **Federal Register**. The notice will also announce that the drug is relisted, under § 314.162(c). The notice will also serve to reinstate approval of all suspended abbreviated new drug applications that referred to the listed drug.

§ 314.162 Removal of a drug product from the list.

(a) FDA will remove a previously approved new drug product from the list for the period stated when:

(1) The agency withdraws or suspends approval of a new drug application or an abbreviated new drug application under § 314.150(a) or § 314.151 or under the imminent hazard authority of section 505(e) of the act, for the same period as the withdrawal or suspension of the application; or

(2) The agency, in accordance with the procedures in § 314.153(b) or § 314.161, issues a final decision stating that the listed drug was withdrawn from sale for safety or effectiveness reasons, or suspended under § 314.153(b), until the agency determines that the withdrawal from the market has ceased or is not for safety or effectiveness reasons.

(b) FDA will publish in the **Federal Register** a notice announcing the removal of a drug from the list.

(c) At the end of the period specified in paragraph (a)(1) or (a)(2) of this section, FDA will relist a drug that has been removed from the list. The agency will publish in the **Federal Register** a notice announcing the relisting of the drug.

41. Section 314.200 is amended by revising the introductory text of paragraph (a), paragraphs (b)(1) and (b)(2), the last sentence in paragraph (c)(1), paragraph (c)(3), and the first sentence in paragraph (g)(1) to read as follows:

§ 314.200 Notice of opportunity for hearing; notice of participation and request for hearing; grant or denial of hearing.

(a) *Notice of opportunity for hearing.* The Director of the Center for Drug Evaluation and Research, Food and Drug Administration, will give the applicant, and all other persons who manufacture or distribute identical, related, or similar drug products as defined in § 310.6 of this chapter, notice and an opportunity for a hearing on the Center's proposal to refuse to approve an application or to withdraw the approval of an application or abbreviated application under section 505(e) of the act. The notice will state the reasons for the action and the proposed grounds for the order.

* * * * *

(b) * * *

(1) To any person who has submitted an application or abbreviated application, by delivering the notice in person or by sending it by registered or certified mail to the last address shown in the application or abbreviated application.

(2) To any person who has not submitted an application or abbreviated application but who is subject to the notice under § 310.6 of this chapter, by publication of the notice in the **Federal Register**.

(c)(1) * * * The applicant, or other person, may incorporate by reference the raw data underlying a study if the data were previously submitted to FDA as part of an application, abbreviated application, or other report.

* * * * *

(3) Any other interested person who is not subject to the notice of opportunity for a hearing may also submit comments on the proposal to withdraw approval of the application or abbreviated application. The comments are requested to be submitted within the time and under the conditions specified in this section.

* * * * *

(g) * * *

(1) Where a specific notice of opportunity for hearing (as defined in paragraph (a)(1) of this section) is used, the Commissioner will enter summary judgment against a person who requests a hearing, making findings and conclusions, denying a hearing, if it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or abbreviated application or the withdrawal of approval of the application or abbreviated application; for example, no adequate and well-controlled clinical investigations meeting each of the precise elements of § 314.126 and, for a combination drug product, § 300.50 of this chapter, showing effectiveness have been identified. * * *

* * * * *

42. Section 314.430 is amended by revising the section heading, paragraphs (a), (b), (c), and (d), the introductory text of paragraph (e), paragraphs (f)(5) and (f)(6), and the introductory text of paragraph (g) to read as follows:

§ 314.430 Availability for public disclosure of data and information in an application or abbreviated application.

(a) The Food and Drug Administration will determine the public availability of any part of an application or abbreviated application under this section and part 20 of this chapter. For purposes of this section, the application or abbreviated application includes all data and information submitted with or incorporated by reference in the application or abbreviated application, including investigational new drug applications, drug master files under § 314.420, supplements submitted under § 314.70 or § 314.97, reports under § 314.80 or § 314.98, and other submissions. For purposes of this section, safety and effectiveness data include all studies and tests of a drug on animals and humans and all studies and tests of the drug for identity, stability, purity, potency, and bioavailability.

(b) FDA will not publicly disclose the existence of an application or abbreviated application before an approvable letter is sent to the applicant under § 314.110, unless the existence of the application or abbreviated application has been previously publicly disclosed or acknowledged. The Center for Drug Evaluation and Research will maintain and make available for public disclosure a list of applications or abbreviated applications for which the agency has sent an approvable letter to the applicant.

(c) If the existence of an unapproved application or abbreviated application has not been publicly disclosed or acknowledged, no data or information in the application or abbreviated application is available for public disclosure.

(d) If the existence of an application or abbreviated application has been publicly disclosed or acknowledged before the agency sends an approval letter to the applicant, no data or information contained in the application or abbreviated application is available for public disclosure before the agency sends an approval letter, but the Commissioner may, in his or her discretion, disclose a summary of selected portions of the safety and effectiveness data that are appropriate for public consideration of a specific pending issue; for example, for consideration of an open session of an FDA advisory committee.

(e) After FDA sends an approval letter to the applicant, the following data and information in the application or abbreviated application are immediately available for public disclosure, unless the applicant shows that extraordinary circumstances exist. A list of approved applications and abbreviated applications, entitled "Approved Drug Products with Therapeutic Equivalence Evaluations," is available from the Government Printing Office, Washington, DC 20402. This list is updated monthly.

* * * * *

(f) * * *

(5) For applications submitted under section 505(b) of the act, the effective date of the approval of the first abbreviated application submitted under section 505(j) of the act which refers to such drug, or the date on which the approval of an abbreviated application under section 505(j) of the act which refers to such drug could be made effective if such an abbreviated application had been submitted.

(6) For applications or abbreviated applications submitted under sections 505(j), 506, and 507 of the act, when FDA sends an approval letter to the applicant.

(g) The following data and information in an application or abbreviated application are not available for public disclosure unless they have been previously disclosed to the public as set forth in § 20.81 of this chapter or they relate to a product or ingredient that has been abandoned and they do not represent a trade secret or confidential commercial or financial information under § 20.61 of this chapter:

* * * * *

43. Section 314.440 is amended by revising the section heading, the introductory text of paragraph (a), and paragraphs (a)(1) and (a)(2) to read as follows:

§ 314.440 Addresses for applications and abbreviated applications.

(a) Applicants shall send applications, abbreviated applications, and other correspondence relating to matters covered by this part, except for products listed in paragraph (b) of this section, to the Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, and directed to the appropriate office identified below:

(1) An application under § 314.50 or § 314.54 submitted for filing should be directed to the Document and Records Section, 12420 Parklawn Dr., Rockville, MD 20852. Applicants may obtain folders for binding applications from the Forms and Publications Warehouse, 12100 Parklawn Dr., Rockville, MD 20852. After FDA has filed the application, the agency will inform the applicant which division is responsible for the application. Amendments, supplements, resubmissions, requests for waivers, and other correspondence about an application that has been filed should be directed to the appropriate division.

(2) An abbreviated application under § 314.94, and amendments, supplements, and resubmissions should be directed to the Office of Generic Drugs (HFD–600), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Items sent by parcel post or overnight courier service should be directed to the Office of Generic Drugs (HFD–600), Center for Drug Evaluation and Research, Food and Drug Administration, Metro Park North II, 7500 Standish Place, rm. 150, Rockville, MD 20855. Correspondence not associated with an application should be addressed specifically to the intended office or division and to the person as follows: Center for Drug Evaluation and Research, Food and Drug Administration, Attn: [*insert name of person*], MPN II, HFD–[*insert mail code of office or division*], 5600 Fishers Lane, Rockville, MD 20857. The mail code for the Office of Generic Drugs is HFD–600, the mail code for the Division of Chemistry is HFD–630, and the mail code for the Division of Bioequivalence is HFD–650.

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PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

44. Part 320 is amended by revising the table of contents with the authority citation continuing to read as follows:

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

Subpart A—General Provisions

Authority: Secs. 201, 501, 502, 505, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 355, 357, 371).

45. Section 320.1 is amended by revising paragraphs (a) and (e) to read as follows:

§ 320.1 Definitions.

(a) *Bioavailability* means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

* * * * *

(e) *Bioequivalence* means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain controlled release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active

ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

* * * * *

46. Part 320 is amended by revising the heading for subpart B, revising §§ 320.21, 320.22, 320.23, 320.24, 320.30, and 320.31, and by removing the heading for subpart C to read as follows:

Subpart B—Procedures for Determining the Bioavailability or Bioequivalence of Drug Products

§ 320.21 Requirements for submission of in vivo bioavailability and bioequivalence data.

(a) Any person submitting a full new drug application to the Food and Drug Administration (FDA) shall include in the application either:

(1) Evidence demonstrating the in vivo bioavailability of the drug product that is the subject of the application; or

(2) Information to permit FDA to waive the submission of evidence demonstrating in vivo bioavailability.

(b) Any person submitting an abbreviated new drug application to FDA shall include in the application either:

(1) Evidence demonstrating that the drug product that is the subject of the abbreviated new drug application is bioequivalent to the reference listed drug (defined in § 314.3(b)); or

(2) Information to show that the drug product is bioequivalent to the reference listed drug which would permit FDA to waive the submission of evidence demonstrating bioequivalence as provided in paragraph (f) of this section.

(c) Any person submitting a supplemental application to FDA shall include in the supplemental application the evidence or information set forth in paragraphs (a) and (b) of this section if the supplemental application proposes any of the following changes:

(1) A change in the manufacturing process, including a change in product formulation or dosage strength, beyond the variations provided for in the approved application.

(2) A change in the labeling to provide for a new indication for use of the drug product, if clinical studies are required to support the new indication for use.

(3) A change in the labeling to provide for a new dosage regimen or for an additional dosage regimen for a special patient population, e.g., infants, if clinical studies are required to support the new or additional dosage regimen.

(d) FDA may approve a full new drug application, or a supplemental application proposing any of the changes set forth in paragraph (c) of this section, that does not contain evidence of in vivo bioavailability or information to permit waiver of the requirement for in vivo bioavailability data, if all of the following conditions are met.

(1) The application was under review by FDA on July 7, 1977.

(2) The application is otherwise approvable.

(3) The application agrees to submit, within the time specified by FDA, either:

(i) Evidence demonstrating the in vivo bioavailability of the drug product that is the subject of the application; or

(ii) Information to permit FDA to waive demonstration of in vivo bioavailability.

(e) Evidence demonstrating the in vivo bioavailability and bioequivalence of a drug product shall be obtained using one of the approaches for determining bioavailability set forth in § 320.24.

(f) Information to permit FDA to waive the submission of evidence demonstrating the in vivo bioavailability or bioequivalence shall meet the criteria set forth in § 320.24.

(g) Any person holding an approved full or abbreviated new drug application shall submit to FDA a supplemental application containing new evidence demonstrating the in vivo bioavailability or bioequivalence of the drug product that is the subject of the application if notified by FDA that:

(1) There are data demonstrating that the dosage regimen in the labeling is based on incorrect assumptions or facts regarding the pharmacokinetics of the drug product and that following this dosage regimen could potentially result in subtherapeutic or toxic levels; or

(2) There are data demonstrating significant intra-batch and batch-to-batch variability, e.g., plus or minus 25 percent, in the bioavailability of the drug product.

(h) The requirements of this section regarding the submission of evidence demonstrating in vivo bioavailability and bioequivalence apply only to a full or abbreviated new drug application or a supplemental application for a finished dosage formulation.

§ 320.22 Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.

(a) Any person submitting a full or abbreviated new drug application, or a supplemental application proposing any of the changes set forth in § 320.21(c), may request FDA to waive the requirement for the submission of evidence demonstrating the in vivo bioavailability or bioequivalence of the drug product that is the subject of the application. An applicant shall submit a request for waiver with the application. Except as provided in paragraph (g) of this section, FDA shall waive the requirement for the submission of evidence of in vivo bioavailability or bioequivalence if the drug product meets any of the provisions of paragraphs (b), (c), (d), or (e) of this section.

(b) For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability or bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) The drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application.

(2) The drug product:

(i) Is administered by inhalation as a gas, e.g., a medicinal or an inhalation anesthetic; and

(ii) Contains an active ingredient in the same dosage form as a drug product that is the subject of an approved full new drug application.

(3) The drug product:

(i) Is a solution for application to the skin, an oral solution, elixir, syrup, tincture, or similar other solubilized form.

(ii) Contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application; and

(iii) Contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application that may significantly affect absorption of the active drug ingredient or active moiety.

(c) FDA shall waive the requirement for the submission of evidence demonstrating the in vivo bioavailability of a solid oral dosage form (other than an enteric coated or controlled release dosage form) of a drug product determined to be effective for at least one indication in a Drug Efficacy Study Implementation notice or which is identical, related, or similar to such a drug product under § 310.6 of this chapter unless FDA has evaluated the

drug product under the criteria set forth in § 320.32, included the drug product in the Approved Drug Products with Therapeutic Equivalence Evaluations List, and rated the drug product as having a known or potential bioequivalence problem. A drug product so rated reflects a determination by FDA that an in vivo bioequivalence study is required.

(d) For certain drug products, bioavailability or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo data. FDA shall waive the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability of the drug product if the drug product meets one of the following criteria:

(1) [Reserved]

(2) The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and the conditions in paragraphs (d)(2)(i) through (d)(2)(iii) of this section are met:

(i) The bioavailability of this other drug product has been demonstrated;

(ii) Both drug products meet an appropriate in vitro test approved by FDA; and

(iii) The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.

(iv) This subparagraph does not apply to enteric coated or controlled release dosage forms.

(3) The drug product is, on the basis of scientific evidence submitted in the application, shown to meet an in vitro test that has been correlated with in vivo data.

(4) The drug product is a reformulated product that is identical, except for a different color, flavor, or preservative that could not affect the bioavailability of the reformulated product, to another drug product for which the same manufacturer has obtained approval and the following conditions are met:

(i) The bioavailability of the other product has been demonstrated; and

(ii) Both drug products meet an appropriate in vitro test approved by FDA.

(e) FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability if waiver is compatible with the protection of the public health. For full new drug applications, FDA may defer a requirement for the submission of evidence of in vivo bioavailability if deferral is compatible with the protection of the public health.

(f) FDA, for good cause, may require evidence of in vivo bioavailability or bioequivalence for any drug product if the agency determines that any difference between the drug product and a listed drug may affect the bioavailability or bioequivalence of the drug product.

§ 320.23 Basis for demonstrating in vivo bioavailability or bioequivalence.

(a)(1) The in vivo bioavailability of a drug product is demonstrated if the product's rate and extent of absorption, as determined by comparison of measured parameters, e.g., concentration of the active drug ingredient in the blood, urinary excretion rates, or pharmacological effects, do not indicate a significant difference from the reference material's rate and extent of absorption. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

(2) Statistical techniques used shall be of sufficient sensitivity to detect differences in rate and extent of absorption that are not attributable to subject variability.

(3) A drug product that differs from the reference material in its rate of absorption, but not in its extent of absorption, may be considered to be bioavailable if the difference in the rate of absorption is intentional, is appropriately reflected in the labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug product.

(b) Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, and are considered medically insignificant for the particular drug product studied.

§ 320.24 Types of evidence to establish bioavailability or bioequivalence.

(a) Bioavailability or bioequivalence may be determined by several in vivo and in vitro methods. FDA may require in vivo or in vitro testing, or both, to establish the bioavailability of a drug product or the bioequivalence of specific drug products. Information on bioequivalence requirements for specific products is included in the current edition of FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" and any current supplement to the publication. The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of demonstrating bioavailability or bioequivalence, as appropriate, for the product being tested.

(b) The following in vivo and in vitro approaches, in descending order of accuracy, sensitivity, and reproducibility, are acceptable for determining the bioavailability or bioequivalence of a drug product.

(1)(i) An in vivo test in humans in which the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time. This approach is particularly applicable to dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution within the body; or

(ii) An in vitro test that has been correlated with and is predictive of human in vivo bioavailability data; or

(iii) An in vivo test in animals that has been correlated with and is predictive of human bioavailability data.

(2) An in vivo test in humans in which the urinary excretion of the active moiety, and, when appropriate, its active metabolite(s), are measured as a function of time. The intervals at which measurements are taken should ordinarily be as short as possible so that the measure of the rate of elimination is as accurate as possible. Depending on the nature of the drug product, this approach may be applicable to the category of dosage forms described in paragraph (b)(1)(i) of this section. This method is not appropriate where urinary

excretion is not a significant mechanism of elimination.

(3) An in vivo test in humans in which an appropriate acute pharmacological effect of the active moiety, and, when appropriate, its active metabolite(s), are measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility. This approach is applicable to the category of dosage forms described in paragraph (b)(1)(i) of this section only when appropriate methods are not available for measurement of the concentration of the moiety, and, when appropriate, its active metabolite(s), in biological fluids or excretory products but a method is available for the measurement of an appropriate acute pharmacological effect. This approach may be particularly applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution.

(4) Well-controlled clinical trials in humans that establish the safety and effectiveness of the drug product, for purposes of establishing bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence. This approach is the least accurate, sensitive, and reproducible of the general approaches for determining bioavailability or bioequivalence. For dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution, this approach may be considered acceptable only when analytical methods cannot be developed to permit use of one of the approaches outlined in paragraphs (b)(1)(i) and (b)(2) of this section, when the approaches described in paragraphs (b)(1)(ii), (b)(1)(iii), and (b)(3) of this section are not available. Ths approach may also be considered sufficiently accurate for determining the bioavailability or bioequivalence of dosage forms intended to deliver the active moiety locally, e.g., topical preparations for the skin, eye, and mucous membranes; oral dosage forms not intended to be absorbed, e.g., an antacid or radiopaque medium; and bronchodilators administered by inhalation if the onset and duration of pharmacological activity are defined.

(5) A currently available in vitro test acceptable to FDA (unusually a dissolution rate test) that ensures human in vivo bioavailability.

(6) Any other approach deemed adequate by FDA to establish bioavailability or bioequivalence.

(c) FDA may, notwithstanding prior requirements for establishing bioavailability or bioequivalence, require in vivo testing in humans of a product at any time if the agency has evidence that the product:

(1) May not produce therapeutic effects comparable to a pharmaceutical equivalent or alternative with which it is intended to be used interchangeably;

(2) May not be bioequivalent to a pharmaceutical equivalent or alternative with which it is intended to be used interchangeably; or

(3) Has greater than anticipated potential toxicity related to pharmacokinetic or other characteristics.

§ 320.30 Inquiries regarding bioavailability and bioequivalence requirements and review of protocols by the Food and Drug Administration.

(a) The Commissioner of Food and Drugs strongly recommends that, to avoid the conduct of an improper study and unnecessary human research, any person planning to conduct a bioavailability or bioequivalence study submit the proposed protocol for the study to FDA for review prior to the initiation of the study.

(b) FDA may review a proposed protocol for a bioavailability or bioequivalence study and will offer advice with respect to whether the following conditions are met:

(1) The design of the proposed bioavailability or bioequivalence study is appropriate.

(2) The reference material to be used in the bioavailability or bioequivalence study is appropriate.

(3) The proposed chemical and statistical analytical methods are adequate.

(c)(1) General inquiries relating to in vivo bioavailability requirements and methodology shall be submitted to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Biopharmaceutics (HFD–420), 5600 Fishers Lane, Rockville, MD 20857.

(2) General inquiries relating to bioequivalence requirements and methodology shall be submitted to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Bioequivalence (HFD–650), 5600 Fishers Lane, Rockville, MD 20857.

§ 320.31 Applicability of requirements regarding an "Investigational New Drug Application."

(a) Any person planning to conduct an in vivo bioavailability or bioequivalence study in humans shall submit an "Investigational New Drug Application" (IND) if:

(1) The test product contains a new chemical entity as defined in § 314.108(a) of this chapter; or

(2) The study involves a radioactively labeled drug product; or

(3) The study involves a cytotoxic drug product.

(b) Any person planning to conduct a bioavailability study in humans using a drug product that contains an already approved, non-new chemical entity shall submit an IND if the study is one of the following:

(1) A single-dose study in normal subjects or patients where either the maximum single or total daily dose exceeds that specified in the labeling of the drug product that is the subject of an approved new drug application or abbreviated new drug application.

(2) A multiple-dose study in normal subjects or patients where either the single or total daily dose exceeds that specified in the labeling of the drug product that is the subject of an approved new drug application or abbreviated new drug application.

(3) A multiple-dose study on a controlled release product on which no single-dose study has been completed.

(c) The provisions of part 312 of this chapter are applicable to any bioavailability or bioequivalence study conducted under an IND.

(d) [Reserved]

(e) [Reserved]

(f) An in vivo bioavailability or bioequivalence study in humans shall be conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter, and informed consent set forth in part 50 of this chapter, regardless of whether the study is conducted under an IND.

§ 320.32 [Redesignated as § 320.38]

47. Section 320.32 *Retention of bioavailability samples* is redesignated as § 320.38.

§ 320.50 [Removed]

48. Section 320.50 *Purpose* is removed.

§ 320.51 [Redesignated as § 320.32]

49. Section 320.51 is redesignated as § 320.32 in subpart B and is revised to read as follows:

§ 320.32 Procedures for establishing or amending a bioequivalence requirement.

(a) The Food and Drug Administration, on its own initiative or in response to a petition by an interested person, may propose and promulgate a regulation to establish a bioequivalence requirement for a product not subject to section 505(j) of the act if it finds there is well-documented evidence that specific

pharmaceutical equivalents or pharmaceutical alternatives intended to be used interchangeably for the same therapeutic effect:

(1) Are not bioequivalent drug products; or

(2) May not be bioequivalent drug products based on the criteria set forth in § 320.33; or

(3) May not be bioequivalent drug products because they are members of a class of drug products that have close structural similarity and similar physicochemical or pharmacokinetic properties to other drug products in the same class that FDA finds are not bioequivalent drug products.

(b) FDA shall include in a proposed rule to establish a bioequivalence requirement the evidence and criteria set forth in § 320.33 that are to be considered in determining whether to issue the proposal. If the rulemaking is proposed in response to a petition, FDA shall include in the proposal a summary and analysis of the relevant information that was submitted in the petition as well as other available information to support the establishment of a bioequivalence requirement.

(c) FDA, on its own initiative or in response to a petition by an interested person, may propose and promulgate an amendment to a bioequivalence requirement established under this subpart.

§ 320.52 [Redesignated as § 320.33]

50. Section 320.52 is redesignated as § 320.33 in subpart B, and the section heading and the introductory paragraph are revised to read as follows:

§ 320.33 Criteria and evidence to assess actual or potential bioequivalence problems.

The Commissioner of Food and Drugs shall consider the following factors, when supported by well-documented evidence, to identify specific pharmaceutical equivalents and pharmaceutical alternatives that are not or may not be bioequivalent drug products.

* * * * *

§ 320.53 [Removed]

51. Section 320.53 *Types of bioequivalence requirements* is removed.

§ 320.54 [Removed]

52. Section 320.54 *Contents of a petition to establish a bioequivalence requirement* is removed.

§§ 320.55 and 320.56 [Redesignated as §§ 320.34 and 320.35]

53. Section 320.55 *Requirements for batch testing and certification by the Food and Drug Administration* and § 320.56 *Requirements for in vitro testing of each batch* are redesignated as §§ 320.34 and 320.35 in subpart B, respectively.

§ 320.57 [Removed]

54. Section 320.57 *Requirements for the conduct of in vivo bioequivalence testing in humans* is removed.

§ 320.58 [Removed]

55. Section 320.58 *Requirements for marketing a drug product subject to a bioequivalence requirement* is removed.

§ 320.59 [Removed]

56. Section 320.59 *Bioequivalence requirements based on data voluntarily submitted* is removed.

§ 320.60 [Removed]

57. Section 320.60 *Bioequivalence requirements for a drug product subject to an old drug monograph* is removed.

§ 320.61 [Removed]

58. Section 320.61 *Requirements for in vivo testing of a drug product not meeting an in vitro bioequivalance standard is removed.*

§ 320.62 [Redesignated as § 320.36]

59. Section 320.62 *Requirements for maintenance of records of bioequivalence testing* is redesignated as § 320.36 in subpart B.

PART 433—EXEMPTIONS FROM ANTIBIOTIC CERTIFICATION AND LABELING REQUIREMENTS

60. The authority citation for 21 CFR part 433 continues to read as follows:

Authority: Secs. 502, 505, 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352, 355, 357).

§ 433.1 [Amended]

61. Section 433.1 *Exemption of antibiotic drugs for human use from batch certification requirements* is amended in paragraph (d)(2) by removing "§ 314.55" and replacing it with "§ 314.94".

Dated: July 17, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

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