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Part II

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 10, 310, 314, and 320
Abbreviated New Drug Application Regulations; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 10, 310, 314, and 320

[Docket No. 85N-0214]

RIN 0905-AB63

Abbreviated New Drug Application Regulations

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing regulations to implement Title I of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417), which amends section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355). The proposal provides for the submission of abbreviated new drug applications for generic versions of drug products first approved after 1962. Before enactment of Pub. L. 98-417 abbreviated applications were permitted under FDA regulations for generic versions of drug products first approved between 1938 and 1962. These new provisions will benefit consumers by making generic drug products available more quickly.

DATES: Comments by October 10, 1989. FDA proposes that any final rule based on this proposal would become effective 60 days after its publication in the **Federal Register.**

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857

FOR FURTHER INFORMATION CONTACT: Marilyn L. Watson, Center for Drug Evaluation and Research (HFD-360), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857 301-295-8038.

SUPPLEMENTARY INFORMATION:

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I. Introduction

On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417). Title I of the law amended the Federal Food, Drug, and Cosmetic Act (the act) to expand the universe of drugs for which FDA would accept abbreviated new drug applications (ANDA s). Before enactment of Pub. L. 98-417 ANDA's were permitted under FDA regulations for duplicates, i.e., generic (different manufacturers') versions, only of drug products first approved between 1938 and 1962. The term "duplicate" applied to a drug product that was the same as an already approved drug product in dosage form, route of administration, kind and amount of active ingredient, indication(s), and any other conditions of use. The regulations permitted ANDA's for "similar" and "related" products only if FDA had made a separate finding, following a manufacturer's petition, that an ANDA was appropriate for that product. Title I provides for the submission of ANDA's for duplicates and certain related versions of drug products previously approved by FDA for safety and effectiveness and listed in the approved drug product list published by the agency. Title I further makes the existence of a patent on an approved drug a factor in the approval of generic copies of that drug, and establishes a system (the so-called "exclusivity provisions") for rewarding research associated with significant innovation by providing for a delay in the submission or effective approval date of certain generic applications.

Title II of Pub. L. 98-417 amended the patent law to provide for the extension, under certain circumstances, of the normal 17-year term of a product, use, or process patent of a patented product which is subject to premarketing clearance.

The proposed rule set forth below, if adopted as a final rule, will implement Title I of Pub. L. 98-417 Final regulations implementing the provisions of Title II of the law were published in the **Federal Register** of March 7 1988 (53 FR 7298). It should be noted that although antibiotics are expressly covered by Title II, they are not covered by Title I. Title I applies only to drugs approved under section 505 of the act (21 U.S.C. 355). Antibiotics are approved under section 507 of the act (21 U.S.C. 357). This proposed rule would, however, reorganize the current regulations governing the abbreviated antibiotic application procedures by placing them in a new subpart.

II. Background

The act as passed by Congress in 1938 established a system of premarket clearance for drugs under which applicants seeking drug approval were required to submit to FDA a new drug application containing, among other things, data showing the drug's safety. (Sections 201(p)(1) and 505(a) as enacted (21 U.S.C. 321(p) and 355(a)).) The law at that time provided that a new drug application 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 products for which a new drug application had become effective, many products were marketed without effective applications that were

identical, similar, or related to products with effective applications. Manufacturers of such products either had concluded that their products were generally recognized as safe, or had received advisory opinions from the agency that a new drug application was not required because their products were generally recognized as safe (i.e., were not "new drugs").

In 1962, Congress amended the drug approval provisions of the act to require affirmative approval of new drug applications before marketing. That approval was to be granted on the basis of a showing that a drug product was not only safe but also effective. (Pub. L. 87-781 (October 10, 1962).) Thus, on or after October 10, 1962, a new drug could not be marketed without an approved new drug application that contained, in addition to safety data, substantial evidence establishing that the drug was effective for its intended uses (21 U.S.C. 355(d)).

Under the 1962 amendments, new drug applications that had become effective before the effective date of those amendments were "deemed" approved. The requirement that drugs be shown to be effective for their intended uses was also made applicable to drugs that had been deemed approved. To implement this Congressional mandate, FDA undertook a program to evaluate the drugs that had been deemed approved to determine whether there was substantial evidence of their effectiveness, as the law required. The systematic evaluation of these drugs and the implementation of the findings of this evaluation became known as the Drug Efficacy Study Implementation (DESI). Under this program, FDA contracted with the National Academy of Sciences/National Research Council (NAS/NRC), which established panels of experts to review available evidence of effectiveness and to provide recommendations to the agency. FDA considered the NAS/NRC panels' recommendations about the effectiveness of these DESI drugs, and announced the agency's conclusions in **Federal Register** notices. These notices, referred to as DESI notices, set forth the acceptable marketing conditions for the class of products covered by the notice. The DESI review covered over 4,000 specific products which had had new drug applications evaluated for safety only and had been allowed to become effective between 1938 and 1962.

A. The Abbreviated New Drug Application (ANDA) Procedure for Pre-1962 Drugs

If a manufacturer had a pre-1962 new drug application 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. As noted above, however, there were many drug products on the market that were identical in active ingredients and indications or very similar to the drug products found effective in the DESI review but for which no new drug application had ever been submitted. 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 new drug application before it could be legally marketed. *United States v. Generix Drug Corp.*, 460 U.S. 453 (1983) (act's definition of "new drug" applies to the drug product rather than to the generic active ingredient). In addition, FDA issued a statement of policy that revoked the earlier advisory opinions that drugs could be marketed without preclearance by the agency. The statement of policy was published in the **Federal Register** of May 28, 1968 (33 FR 7758), and later codified at 21 CFR 310.100.

To provide an appropriate procedure for approval of duplicate products in reliance on the DESI evaluation, a procedure for submission of ANDA's was established (34 FR 2673 (February 27 1969); 35 FR 6574 (April 24, 1970)). After FDA had found through the DESI review that a particular drug product was effective and suitable for ANDA's, FDA published in the **Federal Register** a DESI notice announcing these conclusions; any manufacturer of a duplicate of the drug not already holding an approved new drug application was then required to submit an ANDA to obtain approval to market the duplicate version of the approved drug (35 FR 11273; July 14, 1970).

The approval of an ANDA before passage of Pub. L. 98-417 was based on the theory that the evidence of effectiveness necessary for approval of a new drug application had been provided, reviewed, and accepted during the DESI process. The evidence of safety of the drug had been determined on the basis of information included in the pioneer new drug application and by the subsequent marketing experience with the drug. The information currently required to be in an ANDA is specified in FDA's regulations in 21 CFR 314.55(e) and consists of information showing the applicant's ability to manufacture a product of acceptable quality that will be equivalent in its effectiveness and safety to the drug product whose safety and effectiveness is established. The ANDA thus contains information on the drug product's formulation, manufacture, quality control procedures, and labeling. In addition, the DESI notice may identify other information that FDA requires in an ANDA for a specific drug product, usually data on the bioavailability of the product showing that it is similar to that of a standard product. The ANDA, therefore, provides for agency review of the same kind of product quality information required in a full new drug application but omits the reports of investigations establishing the safety and effectiveness of the drug which are already established.

B. Procedure for Duplicates of Post-1962 Drugs ("Paper NDA Policy)

FDA's ANDA policy established for pre-1962 drugs was never extended to duplicates of drugs first approved for marketing on or after October 10, 1962. The agency long recognized the value of an ANDA system for the post-1962 drugs and at various times considered and announced the possibility of establishing such a system either by regulation or through legislation (see, e.g., Drug Regulation Reform Act of 1978 (95th Cong., 2d Sess. (1978), Drug Regulation Reform Act of 1979 (96th Cong., 1st Sess. (1979), and proposed rule of September 1, 1978 (43 FR 39126)). During the 1970's and early 1980's, patents expired for many post-1962 drugs, including some high volume, therapeutically important drugs. As a result, many drug manufacturers became increasingly interested in changing FDA's new drug approval system to permit the submission of ANDA s for duplicate versions of post-1962 drugs.

FDA did allow some duplicate drug products of drugs first marketed after 1962 to be marketed under FDA's "paper NDA policy. (See 46 FR 27396; May 19, 1981, publication of "Paper NDA memorandum.) Under that policy, FDA could approve new drug applications for post-1962 duplicate drug products on the basis of evidence of safety and effectiveness derived primarily from published reports, if those reports were of well-controlled studies, thus eliminating the need for manufacturers to perform most of their own tests. Although the courts upheld the legality of paper NDA's (see, e.g., *Burroughs Wellcome Co. v. Schweiker*, 649 F.2d 221 (4th Cir. 1981)), adequate literature, including detailed reports of adequate and well-controlled studies, was available for only a fraction of post-1962 drugs. Moreover, the staff effort involved in reviewing paper NDA s for

drugs that were already available and whose evidence of safety and effectiveness was already well documented in a prior application was a substantial and wasteful use of agency resources.

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

Beginning in 1978, Congress considered various forms of legislation that would have expressly authorized an ANDA procedure for duplicate versions of post-1962 drugs, and, concurrently, legislation to restore patent life lost during the new drug approval process. In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) which became law on September 24, 1984. The new law consists of two titles. Title I authorizes approval of generic new drugs and Title II authorizes extension of patent terms for approved new drugs. The two parts of the bill were intended to provide a careful balance between promoting competition among pioneer or brand-name and generic drugs, and encouraging research and innovation. The ANDA provisions of Title I provide for approval of duplicate or related versions of approved drugs whose patents have expired, and that have been shown through the ANDA approval requirements to be as safe and effective as their brand name counterparts, but without the submission of duplicative safety and effectiveness data. Thus, these provisions are intended to encourage competition by decreasing the time and expense of bringing generic drugs to market, and thereby to provide the public with low cost drugs.

The patent term extension provisions of Title II provide for the extension of drug patent terms beyond the normal 17 years to reflect the period of patent life lost during FDA's review of safety and effectiveness data for the drug. These extensions of patent life are intended to encourage the innovation necessary for the development of important new drug products, by increasing the period during which innovative products are protected from competition.

Title I specifically amends only the new drug provisions of the act at section 505 and applies only to nonantibiotic human drugs submitted and approved under section 505 of the act. The statutory authority for approving antibiotics, including generic antibiotics and antibiotics in combination with other antibiotics or nonantibiotic active ingredients, is section 507 of the act. Therefore, Title I does not apply to antibiotics. Title I does, however, apply to new drugs containing insulin. Although certified under section 506 of the act (21 U.S.C. 356), insulin-containing products are approved under section 505 of the act.

Section 505(j) of the act, as amended by the 1984 Amendments, establishes a statutory ANDA procedure for duplicate and related versions of previously approved pioneer drug products, in which Congress intended to adopt with few modifications the policies developed by FDA in the agency's approval of ANDA's for pre-1962 drugs. Section 505(b)(1) of the act, as amended, requires that certain patent information be submitted to FDA for all previously approved new drug applications, all newly submitted applications, and all applications previously submitted but not yet approved. Section 505(b)(2) of the act, as amended, provides 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 the applicant and for which the applicant has not obtained a right of reference or use from the person who conducted the investigations.

Section 505(l) of the act establishes rules for the public disclosure of safety and effectiveness data submitted as part of a new drug application.

The new law also provides patent protection for the developer of pioneer new drugs by delaying the effective date of approval of an ANDA or 505(b)(2) application until all relevant product and use patents for the pioneer drug have expired, or until the patent owner is notified of, and given an opportunity to litigate, a challenge to such patents. In addition, for new chemical entities (active moieties never before approved in the U.S.) and significant innovations in already approved chemical entities, the law prohibits the submission or delays the effective date of approval of an ANDA or 505(b)(2) application during specified periods that are independent of the patent status of the pioneer drug.

The 1984 Amendments require FDA to promulgate new implementing regulations. The new law further provides that, until such time as FDA has new implementing regulations in effect, the currently existing regulations or ANDA's under § 314.55 (formerly § 314.2) will be effective, absent a conflict with the new law.

In the **Federal Register** of May 24, 1985 (50 FR 21460), FDA published a notice requesting public comment on Title I of Pub. L. 98-417 The notice also announced the establishment of a public file (Docket No. 85N-0214) for all comments, views, and other information submitted to FDA concerning Title I. The purpose of the notice was to obtain public comment on interpretation of the new law to assist the agency in its regulation writing process. In the **Federal Register** of August 7 1985 (50 FR 31887), FDA published a notice reopening for an unspecified period of time the period for public comment on Title I. Interested persons may now focus their comments on this proposed rule during the 90 day comment period on the proposal. Therefore, the period of time for comment on Title I under the August 7 notice ends on July 10, 1989.

Since passage of the 1984 Amendments, FDA has issued a series of letters to NDA and ANDA holders and applicants offering interim guidance on the more controversial provisions of the new law. Copies of these letters are in a public file under Docket No. 85N-0214. To the extent that the provisions of this proposed rule differ from the guidance in these letters, this proposed rule supersedes the previous guidance.

D. Relationship to New Drug Regulations

In the **Federal Register** of February 22, 1985 (50 FR 7452), FDA published revised regulations in 21 CFR Part 314 governing the approval for marketing of new drugs and antibiotic drugs for human use. Those regulations set forth procedures and requirements for the submission to, and the review by, FDA of full applications (NDA's) and abbreviated applications, as well as amendments, supplements, and postmarketing reports to such applications, by persons seeking or holding approval from FDA of an application under section 505 of the act to market a new drug or an application under section 507 of the act to market an antibiotic drug. Those regulations were not intended to implement the 1984 Amendments to the act. (See 50 FR 7466.) The provisions of this proposed rule further revise 21 CFR Part 314 to implement the 1984 Amendments.

III. Highlights of This Proposal

This proposed rule would (1) reorganize and revise 21 CFR Part 314 to incorporate the new requirements and procedures imposed upon applicants by the 1984 Amendments, and (2) revise 21 CFR Part 320 consistent with the bioequivalence requirements of the 1984 Amendments and current agency policy. The major provisions implementing the 1984 Amendments are summarized as follows:

A. Abbreviated Applications

New section 505(j) of the act governs the requirements and procedures for ANDA s. Under the statute, an ANDA is permitted for (1) a drug product that is the "same" as a drug product listed in the approved drug product list published by the agency (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. The agency proposes in a new Subpart C to describe the content of and procedures for submission of an ANDA. The proposal would retain the current ANDA format which requires the submission of an archival and review copy of the ANDA. For an ANDA for a drug product that is the "same" as a listed drug, the focus of the proposed requirements is to provide FDA with sufficient information to assure that the drug product for which the applicant is seeking approval (1) is the same as the listed drug referred to by the applicant with respect to active ingredient(s), route of administration, dosage form, strength, and conditions of use, except for those conditions of use that are protected by patent or that have been accorded periods of exclusivity, (2) is bioequivalent to the listed drug, and (3) has the same labeling as that of the listed drug except for changes because the proposed drug has a different manufacturer or distributor. In addition, the regulations would require that the ANDA contain a certification with respect to product and use patents covering the listed drug and information about the applicant's ability to manufacture a drug product of acceptable quality.

B. ANDA Suitability Petitions

The statute provides that an ANDA applicant may petition FDA for permission to file an ANDA under section 505(j)(2)(C) of the act for a drug product that has one different active ingredient (permitted only in a combination product), or whose route of administration, dosage form, or strength differs from that of a listed drug. These are the only types of changes permitted in an ANDA. The proposed rule describes the kinds of information a petitioner must include in its petition to demonstrate to FDA 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 safety and effectiveness of the proposed drug product or that a drug product with a different active ingredient may be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an ANDA.

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

C. 505(b)(2) Applications

In addition to ANDA's, the 1984 Amendments recognize another type of application for an applicant seeking approval of a generic drug: a 505(b)(2) application. Although similar to FDA s "paper NDA policy, section 505(b)(2) of the act has broader applicability. Section 505(b)(2) of the act applies to any application for which the investigations relied on by the applicant to provide the "full reports" of safety and effectiveness required by section 505(b)(1)(A) of the act 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 who conducted the investigations. Thus, section 505(b)(2) of the act covers not only literature-supported NDA's for duplicates of approved drugs, but any NDA's for drug products that rely for approval on studies not conducted by or for the applicant or for which the applicant does not have a right of reference.

Applications described in section 505(b)(2) of the act are submitted under section 505(b)(1) of the act. They are therefore subject to the same statutory provisions that govern full new drug applications. However, the new statutory provisions impose on a 505(b)(2) applicant additional requirements with respect to patent certification, notification of such certification to the patent owner, and exclusivity that are generally the same as those that apply to ANDA's. The agency proposes to include in the regulations requirements applicable to 505(b)(2) applications.

D. Patent Information, Certification, and Notice of Certification to Patent Owner and Certain Application Holders

The statute prohibits the agency from making effective the approval of an ANDA or an application described by section 505(b)(2) of the act before all relevant product and use patents for the listed drug have expired, except where the generic applicant asserts either that its product will not infringe the patent or that the patent is invalid. In the latter case, approval of the ANDA or 505(b)(2) application may not be made effective until the patent owner and NDA holder have been notified and have had an opportunity to litigate the issue of patent infringement or validity. To facilitate the patent protection provisions, the statute requires that applications submitted under section 505(b) of the act include the patent number and expiration date of all relevant product patents that claim the drug in the application or use patents that claim a method of using the drug. The agency publishes this patent information in its approved drug product list for each listed drug for which patent information has been submitted. A generic drug applicant submitting an ANDA that refers to a listed drug must include a certification as to the status of all patents applicable to the listed drug. Similarly, an applicant submitting a 505(b)(2) application must make certifications with respect to patents claiming any listed drug on which investigations that are relied upon by the applicant for approval of its application were conducted or claiming a use for such listed drug. If a generic applicant certifies that a relevant patent expires on a specified date, the effective date of approval of the ANDA or 505(b)(2) application will be delayed until the expiration of the patent. When a generic applicant certifies that any product or use patent is invalid or will not be infringed, the applicant must give notice of such certification to the patent owner and appropriate approved application holder for the listed drug. The generic applicant must include in the notice the factual and legal basis for the applicant's opinion that the patent is invalid or will not be infringed. Finally, a patent owner or NDA holder has 45 days from receipt of the notice of certification to file suit against the generic applicant to defend the patent. If the patent owner or NDA holder files suit within 45 days, the effective date of approval of the ANDA or 505(b)(2) application may be delayed up to 30 months pending resolution of the lawsuit.

The proposed rule describes (1) the requirements for the submission of patent information by a pioneer NDA holder, (2) the patent certification requirements applicable to generic applicants and (3) the content of a patent certification notice. The proposal also specifies (1) when and to whom the notice is to be sent and (2) the effect of each type of patent certification on the effective date of approval of an application for a generic drug product.

E. Exclusivity

Sections 505(j)(4)(D) and 505(c)(3)(D) of the act protect certain listed drugs, or certain changes in listed drugs, from generic copying for specified periods by placing a moratorium on the submission, or by delaying the effective date of approval, of ANDA's and 505(b)(2) applications for those listed drugs. These so-called "exclusivity provisions" provide the following periods of protection from generic competition: (1) a 10-year period of exclusivity for new chemical entities approved during the period January 1, 1982, to September 24, 1984, the date of enactment of the 1984 Amendments; (2) a 5-year period of exclusivity for new chemical entities approved after September 24, 1984; (3) a 3-year period of exclusivity for non-new chemical entities approved after September 24, 1984, if the applicant submitted an application containing reports of "new clinical investigations (other than bioavailability studies) essential to the approval and conducted or sponsored by the applicant"· (4) a 3-year period of exclusivity for certain changes made after September 24, 1984, if the applicant submitted a supplement containing reports of "new clinical investigations (other than bioavailability studies) essential to the approval and conducted or sponsored by the person submitting the application"· and (5) a 2-year period of exclusivity for non-new chemical entities, or for certain changes made to already approved drug products, approved during the period January 1, 1982, to September 24, 1984.

The agency proposes to codify the first four of these five exclusivity provisions; the fifth provision will not be codified because it expired on September 24, 1986. The agency also proposes to define certain terms used in the regulations, and clarify the agency's interpretation of each of the provisions.

F Withdrawal or Suspension of Approval of an ANDA

The statute authorizes the Secretary to remove from the market, by withdrawal or suspension of approval, any generic drugs already approved if the approval of the listed drug referred to by the generic applicant is withdrawn or suspended or if the listed drug is voluntarily withdrawn from sale by its manufacturer for what the agency determines are safety or effectiveness reasons. The agency proposes to establish in the regulations a procedure for the withdrawal or suspension of approval of an ANDA under these circumstances.

IV The List

Section 505(j)(6) of the act requires FDA to publish and make publicly available a list of all drug products approved for safety and effectiveness under section 505(c) or approved under section 505(j) of the act. The agency's publication, Approved Drug Products with Therapeutic Equivalence Evaluations" (the list), and its monthly supplements, are being used to satisfy this statutory requirement. In accordance with section 505(j)(6) of the act, FDA updates the list monthly through publication of cumulative supplements. Under the act, a drug product approved for safety and effectiveness under section 505(c) or approved under section 505(j) is deemed to be a listed drug on the date of its approval even though the drug product is not actually included in the list until the next monthly update of the agency's published list. (See section 505(j)(6)(B) of the act.) A drug will not be listed as eligible for approval under an ANDA for the following reasons: (1) the approval of the drug product has been withdrawn or suspended for grounds described under section 505(e) (1) through (5) or 505(j)(5) of the act, or (2) FDA determines that the drug product has been voluntarily withdrawn from sale by the manufacturer due to safety or effectiveness concerns. (See discussion about removing drugs from listed status at part V section P below.)

Further, the agency will withdraw approval of and remove from the list any drug product that is the subject of a new drug application and that may now be marketed over-the-counter (OTC) pursuant to an effective final OTC monograph. Drug products that conform to an OTC final monograph are considered by the agency to be generally recognized as safe and effective and, as such, are no longer considered to be "new drugs" as defined in section 201(p) of the act. Thus, such products do not require an approved new drug application. In addition, FDA's enforcement policy for prescription drugs undergoing review in the agency's OTC drug review (21 CFR 330.13) permits a prescription drug to be marketed OTC without approval before a final monograph issues in each of the following circumstances: (1) where the drug is classified by an OTC advisory review panel in Category I (generally recognized as safe and effective and not misbranded) and FDA does not dissent in the preamble to the panel report or thereafter, (2) where FDA concludes that a drug that was not classified by a panel in Category I later tentatively qualifies for classification in Category I and so states in a **Federal Register** announcement, and (3) where the agency, on its own initiative, proposes by **Federal Register** announcement OTC marketing of a prescription drug not reviewed by an OTC advisory review panel, and public notice that OTC marketing may commence is issued after a formal comment period on the agency's proposed change.

Section 505(j)(6) of the act also requires FDA to include in the list the date of approval and application number of each drug product approved after 1981, whether in vitro or in vivo bioequivalence studies or both such studies are required for ANDA's for a listed drug, and the patent information required by section 505 (b) or (c) of the act. Although not required by the act, the list, as published, also identifies all drug products that qualify under the act for periods of exclusive marketing, regardless of patent status, and states therapeutic equivalence evaluations for approved multisource prescription drug products. (Information on therapeutic equivalence evaluations is provided under the policy announced in the **Federal Register** of October 31, 1980 (45 FR 72582). These proposed regulations do not modify or affect in any way the policy announced in that notice, nor do they affect any therapeutic equivalence evaluation published in the list.) As a general rule, FDA intends to use the list and its supplemental updates as the primary means of announcing information regarding patent status, exclusivity, type of bioequivalence study needed, and eligibility for consideration in an ANDA.

The list and its supplements are available on an annual subscription basis from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402. In addition, a copy of the list and its supplemental updates will be placed on public display in the Dockets Management Branch (address above) when FDA sends them forward for printing.

V Provisions of This Proposal

FDA proposes to reorganize 21 CFR Part 314 by revoking existing §§ 314.55 and 314.56, which describe the

requirements for abbreviated applications and the drug products for which abbreviated applications are suitable, by adding a new Subpart C, and by redesignating the existing subparts. The agency further proposes to revise existing sections of 21 CFR Part 314, where necessary, to implement the 1984 Amendments. New proposed Subpart C contains regulations on abbreviated applications for new drugs and antibiotics and the responsibilities and rights of applicants concerning their abbreviated applications. As revised, Subpart B would contain regulations on new drug applications submitted under section 505(b) of the act and antibiotic applications other than abbreviated antibiotic applications. FDA proposes to revise existing sections under Subpart B to remove any reference to abbreviated applications. Existing Subparts C through F are redesignated as Subparts D through G, respectively. Because the 1984 Amendments impose new procedural requirements upon applicants submitting ANDA s, FDA believes that placement of these requirements in a separate subpart will make them easier to find, read, and understand.

As noted above, Title I of the 1984 Amendments does not apply to antibiotics. Section 507 of the act, however, already provides for abbreviated applications for duplicates of approved antibiotic drugs. Therefore, except for a proposed revision to the adverse drug experience reporting requirements for new drugs and antibiotics, the agency proposes to retain the current requirements contained in Subpart B for abbreviated antibiotic applications, but restate them in the new Subpart C. (See discussion under part V section G. below.)

A. Definitions

FDA proposes to revise § 314.3(b) to incorporate definitions and interpretations necessary to implement the 1984 Amendments. The regulations would define "abbreviated application to mean the application described under § 314.94, including all amendments and supplements to the application. The term "abbreviated application" applies to both an abbreviated new drug application and an abbreviated antibiotic application. When particular regulations apply to only one of these groups, or to specific drugs, however, the agency will be more specific by referring to an "abbreviated new drug application" or an "abbreviated antibiotic application. The proposed regulations would revise the definition of "application" to mean the application described under § 314.50, including all amendments and supplements to the application.

Proposed revised § 314.3(b) incorporates the statutory description in section 505(b)(2) as the definition of a "505(b)(2) application.

The agency proposes to retain the current definition of "drug product" under § 314.3(b). The agency notes that the term "drug" is used throughout section 505 of the act. For purposes of this proposed rule, FDA interprets the term "drug" to mean "drug product" unless otherwise specified.

The agency proposes to define "listed drug" to mean a new drug product that has been approved for safety and effectiveness under section 505(c) of the act or approved under section 505(j) of the act, the approval of which has not 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. A list of such drugs is published in the current edition of FDA's publication, Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) and any current supplement to the list. A drug product is deemed to be a "listed drug" if it has been approved for safety and effectiveness under section 505(c) of the act or approved under section 505(j) of the act but has not yet been included in the list. For a drug product that is subject to FDA's DESI review, the agency will consider the applicable DESI notice published in the **Federal Register** a listed drug until a drug product subject to the notice meets the conditions for approval of effectiveness set forth in the notice and becomes a listed drug.

FDA recognizes that approved drug products with delayed effective dates, see part V sections K. and L. below, will be considered "listed" drugs to which subsequent ANDA's can refer. The agency believes that permitting such references will, in some cases, conserve agency resources and reduce burdens on ANDA applicants. For example, there will be drug products with delayed effective dates for which changes in dosage form, strength, route of administration or active ingredients were approved pursuant to ANDA suitability petitions. Some of these products will represent beneficial alternatives to, or improvements over, existing drug products. Permitting subsequent ANDA applicants to refer to these drug products with delayed effective dates will eliminate the burden on the subsequent applicants to submit, and FDA to review, duplicative ANDA suitability petitions. However, consistent with the patent protection and exclusivity provisions of the 1984 Amendments, the subsequent applicant's ANDA will generally share the same delayed effective date as the listed drug.

The agency proposes to define "reference listed drug" to mean 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.

The agency proposes to define "the list" to mean the current edition of FDA s publication Approved Drug Products with Therapeutic Equivalence Evaluations" and any current supplement to the publication.

B. Drug.Products for Which Abbreviated Applications May Be Submitted

The agency proposes to revoke existing § 314.56 and propose a new § 314.92 that describes the drug products for which abbreviated applications may be submitted to the agency. As described in proposed § 314.92(a), FDA proposes to accept an abbreviated application for the following drug products:

1. *Duplicates of a listed drug.* Section 505(j) of the act provides for the submission of ANDA's for generic versions (duplicates) of any drug product listed under section 505(j)(6) of the act (hereinafter referred to as a "listed drug"). Thus, an applicant may submit an ANDA for a drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug, so long as its submission is not precluded by exclusivity. (See discussion at part V section L.1.)

Drug products approved after enactment of the 1984 Amendments, but not marketed, or those approved and for which marketing has been discontinued but for which FDA has made no determination that the marketing ceased for reasons of safety or effectiveness will be included in the list, but identified with a special symbol or placed in a special appendix. In addition, some drug products reviewed under DESI and approved for safety and effectiveness and some post 1962 approved drug products are not published in the list because marketing was discontinued before September 24, 1984. Although technically such drug products are listed drugs under section 505(j)(6)(B) of the act, FDA does not intend to update the list retrospectively to include drug products that no longer generate interest with respect to marketing either by the

pioneer applicant or by another applicant. A firm wishing to submit an ANDA for such a listed drug should petition the agency under § 314.122 to relist the drug product and submit information to show that its withdrawal from sale was not for safety or effectiveness reasons. (Also see discussion under part V section 0.1. below.)

2. *Drug Products that differ from a listed drug.* Section 505(j) of the act permits the submission of an ANDA for a drug product that differs from the listed drug if FDA has approved a petition from a prospective applicant requesting the change. The differences from the listed drug for which petitions may be submitted are differences in route of administration, dosage form, and strength, or, when the listed drug contains more than one active ingredient, a change in one of its active ingredients. To alert interested persons to petitions that have been approved permitting the submission of an abbreviated application for a drug product that differs from a listed drug, the agency will publish in the list all approved petitions submitted under section 505(j)(2)(C) of the act and a description of the permitted changes. Subsequent applicants who wish permission to make a change permitted in an already approved petition may refer in their ANDA's to the approved petition rather than filing a duplicative petition. To aid potential petitioners in preparing their petitions, the list also includes all petitions that have been denied. All such petitions are also on public display in FDA's Dockets Management Branch (address above).

3. *Antibiotics.* Section 507(a) of the act permits the submission of abbreviated applications for duplicates of all antibiotics the agency has already approved for marketing. The agency includes approved antibiotic drug products in the list, even though antibiotics are not covered in the 1984 Amendments, and, therefore, are not subject to, for example, the patent certification and exclusivity provisions of the act.

4. *DESI drug products.* Under its DESI program, the agency has accepted ANDA s for drug products that were the same as certain pre-1962 drug products reviewed under the DESI program. Under this program, each **Federal Register** notice announcing that a particular drug has been found effective has included, when appropriate, an FDA finding that an ANDA is the suitable mechanism by which manufacturers or suppliers of the drug product may obtain FDA approval. In addition, an ANDA may be submitted for a drug product that is similar or related to a DESI drug and for which FDA has made a separate finding, in response to a petition, that an ANDA is suitable.

A pre-1962 approved drug product in the DESI review does not qualify for marketing exclusivity under the 1984 Amendments if the applicant seeks only approval of the indications in the DESI notice. However, DESI products for which additional new uses beyond those reviewed in the DESI program are approved may qualify for periods of marketing exclusivity for the new use under certain circumstances.

C. ANDA Suitability Petitions

Proposed § 314.93 would implement section 505(j)(2)(C) of the act. That section of the act permits an applicant to petition the agency for permission to submit an ANDA for a drug product that differs from a listed drug when the change is one authorized by the statute and the agency has granted a petition for the change. Under the proposal, an applicant may petition FDA for permission to submit an ANDA for a drug product that differs from a listed drug in route of administration, dosage form, or strength. If a proposed drug product were more bioavailable than the innovator's product and the applicant proposed to reduce the dose to a level that delivered plasma levels equivalent to the innovator's product, a petition for a change in strength would be permitted.

In addition, an applicant may seek to change one of the active ingredients of the listed drug when the listed drug is a combination product. For example, the agency may find acceptable the substitution of one analgesic for another, e.g., acetaminophen for aspirin, in a combination product. The active ingredient the applicant wishes to substitute in its product must be approved for safety and effectiveness in a listed drug or must be an ingredient of a drug product that does not meet the definition of "new drug" under section 201(p) of the act. The remaining active ingredients of the combination product, however, must be identical to the other active ingredients of the reference listed drug. (See discussion at part V section D.1.c. below.)

An applicant is not permitted to petition for any other kinds of changes from listed drugs. H. Rept. 98–857 Part 1, 98th Cong., 2d Sess. at 23 (1984). Thus, for example, an applicant may not petition to submit an ANDA for a different active ingredient in a single active ingredient drug product, for an extra active ingredient in a combination product, or for a new use for an already approved drug product. The legislative history of the 1984 Amendments supports the agency's position that a different active ingredient may be substituted only in a combination drug product. Part 1 of the House Report describes FDA's authority to grant petitions requesting changes from listed drugs:

> If an applicant wishes to vary the route of administration, dosage form or strength of the generic drug from the listed drug, it must first petition the FDA for permission to file an ANDA for the differing generic drug. In addition, the applicant may request to vary one of the active ingredients in the generic drug from the listed drug *when the listed drug is a combination product.* The remaining active ingredients of the generic drug must be the same as the other active ingredients of the listed drug.
>
> *These are the only changes from the listed drug for which an applicant may petition.*

H. Rept. 98–857 Part 1, 98th Cong., 2d Sess. 23 (1984) (emphasis added). Section 314.93(e)(1)(ii) requires denial of a petition seeking to change an active ingredient, if the drug that is the subject of the petition is not a combination drug.

FDA considers a salt or ester of an active ingredient to be a different active ingredient, and will not approve petitions that seek permission to submit an ANDA for a drug product which substitutes a different salt or ester of an active ingredient from that of a listed drug, unless the petition seeks a change in a combination product and the new salt or ester has been approved or is not a new drug. No petition is necessary for a change in the inactive ingredients from those of the listed drug.

Proposed § 314.93(d) would require a petitioner to identify a listed drug and include in its petition 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 reference listed drug. A petitioner may, under limited circumstances, identify more than one listed drug, e.g., when the petitioner seeks permission to submit an ANDA for a drug product that substitutes one of the active ingredients in a combination listed drug and the substituted ingredient itself is a listed drug. (Also see discussion under submitting an application for, or a suitability petition that relies on, a listed drug that is no longer marketed at part V section 0.1.)

Sections 505(j)(2)(A)(v) and 505(j)(3)(G) of the act require that the labeling of generic drugs be the "same" as the labeling approved for the listed drug, except where a change in labeling is "required because of differences approved under a petition filed under section 505(j)(2)(C) of the act or because

the drug and the listed drug are produced or distributed by different manufacturers. FDA emphasizes that the exceptions to the requirement of "same labeling" are limited. The agency will not approve a petition under section 505(j)(2)(C) of the act that seeks permission to submit an ANDA for a product with significant changes in labeling (such as new warnings or precautions) intended to address newly introduced safety or effectiveness problems not presented by the listed drug. Such labeling changes are not the kind that were intended to fall within the limited exceptions in sections 505(j)(2)(A)(v) and 505(j)(3)(G) of the act. FDA does not believe that it would be consistent with the purpose of section 505(j) of the act, which is to assure the marketing of generic drugs that are as safe and effective as their brand-name counterparts, to interpret section 505(j)(2)(C) of the act as permitting the marketing of generic drugs with diminished safety or effectiveness and concomitantly heightened labeled warnings. Rather than waste agency resources by approving a petition for a drug that cannot satisfy the ANDA approval requirements, FDA is proposing to deny a suitability petition for a change that would necessitate significant new labeled warnings or precautions.

Under the act, the agency must approve an appropriately submitted petition for a change authorized by the statute, unless it finds (1) that investigations are necessary to show the safety and effectiveness of the drug product or of any of its active ingredients, the route of administration, dosage form, or strength which differ from the listed drug (see section 505(j)(2)(C)(i) of the act), or (2) in reviewing a petition to substitute one of the active ingredients in a combination product, that the safety or effectiveness of the drug product may not be adequately evaluated by the information in an ANDA (see section 505(j)(2)(C)(ii) of the act).

The legislative history of the 1984 Amendments makes clear that section 505(j)(2)(C)(ii) of the act was added to clarify FDA's authority to reject petitions for new combination products that raise safety or effectiveness issues. See H. Rept. 98–857 Part 1, 98th Cong., 2d Sess. 23 (1984); 130 Cong. Rec. H9114 (daily edition September 6, 1984) (statement of Representative Waxman). The agency anticipates that it will only rarely approve petitions to submit ANDA's for new combinations, because data on the safety and effectiveness of the new combinations will almost always be needed. See hearing on S. 2748 before the Committee on Labor and Human Resources, 98th Cong., 2d. Sess. 31–2 (June 28, 1984) (statement of Mark Novitch, Acting Commissioner of Food and Drugs).

Section 314.93(e)(1)(iii) specifies the grounds for denying a petition to change an active ingredient in a combination product. Under the proposal at § 314.93(e)(1)(iii)(B), the agency would not approve a petition to substitute one of the active ingredients in a combination product if the petition failed to 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 could be expected to have the same therapeutic effect as the reference listed drug when administered to patients for a condition of use identical to that of the reference listed drug. Under section 505(j)(2)(A)(iv) of the act, this information is required to be contained in an ANDA for a product with a different active ingredient than the listed drug. (See § 314.94(a)(7) and discussion at Part V section D.1.f.) FDA believes that this information must also be included in a petition to substitute an active ingredient because the ANDA could not be approved without this information and because substitution of an active ingredient of a pharmacological or therapeutic class different from that of the ingredient in the reference listed drug that is to be changed may be presumed to result in a product with a different degree of safety or effectiveness. Such a product would require investigations to show its safety and effectiveness; thus an ANDA would not be appropriate.

The information needed to provide scientific support for the safety and effectiveness of the new combination drug product should consist of well-documented evidence of the general acceptance that the ingredients to be substituted for each other are interchangeable and have known equipotent doses. Such information could be in the form of agency findings or conclusions in previous **Federal Register** notices. For example, FDA has allowed, in appropriate cases, substitution between aspirin and acetaminophen based on extensive scientific data establishing their safety and effectiveness and their equipotent doses and on long-term experience with these ingredients when used in combination with other drugs (see 47 FR 34636 at page 34641; August 10, 1982). If interchangeability is not generally accepted, investigations would be required to establish the safety and effectiveness of the new proposed combination product, and the product would properly be the subject of a new drug application submitted under section 505(b) of the act. New clinical data would not be an appropriate means of establishing that a new combination would have the same therapeutic effect as the listed combination drug because the need to review such data would require denial of the petition.

Sections 314.93(e)(1)(iii) (C) and (D) similarly require denial of a petition if the petition fails to demonstrate that the substituted active ingredient is already approved in a listed drug or is in a drug satisfying the requirements of section 201(p) of the act, or that the remaining active ingredients in the combination are identical to those of the listed combination drug. (See section 505(j)(3)(C) and H. Rept. 98–857 Part 1, *supra*, at 23.) In the absence of information that the safety and effectiveness of the changed ingredient has already been established and that the remaining active ingredients have not also been changed, the safety and effectiveness of the new combination cannot be evaluated without new investigations and thus cannot be the subject of an ANDA.

Under the proposal at § 314.93(e)(1)(v), the agency would not approve a petition that relies on a listed drug that has been voluntarily withdrawn from sale and that has not been referred to in an approved ANDA, unless the agency determines that the withdrawal of the listed drug was not for safety or effectiveness reasons. A generic applicant may obtain approval of a suitability petition to submit an ANDA for a change from a listed drug only when the safety and effectiveness of the listed drug can be relied on to support approval of the change. To assure that ANDA's will not be submitted for drug products that rely on a listed drug whose safety or effectiveness is questionable, the agency will refuse to approve a suitability petition that relies on a listed drug that has been voluntarily withdrawn from sale until the agency can determine that there are no safety or effectiveness concerns about the listed drug.

If the agency approves a petition for a change from a listed drug, FDA may require that certain information supporting the change be included in the ANDA. (See section 505(j)(2)(A) of the act.) The agency may also require additional data concerning the change during its review of an application.

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 ANDA 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. By limited confirmatory testing, the agency means simple studies intended to rule out unlikely problems. For example, data from acute animal studies to show the absence of liver enzyme induction properties of the substituted analgesic active ingredient might be required and be acceptable in a petition. (See 48 FR 2751 at 2753; January 21, 1983, at paragraph 4.) A study intended to answer basic safety or effectiveness questions or one that would require substantial scientific review would not be considered limited confirmatory testing.

A petitioner must use the procedures set forth in § 10.20 (21 CFR 10.20) and the format of a petition established in § 10.30 (21 CFR 10.30). However, unlike a citizen petition under § 10.30, section 505(j)(2)(C) requires FDA to approve or disapprove a petition requesting permission to submit an ANDA for a drug product differing from a listed drug within 90 days of its submission to the agency. Both proposed § 314.93 and proposed revised § 10.30 incorporate this statutory requirement. As is the case under the DESI review in which the hearing opportunity provided by section 505(c) of the act does not apply to ANDA applicants who disagree with an adverse agency decision on whether their products may rely on DESI conclusions, there is no legal right to an opportunity for a hearing on a petition denial under section 505(j)(2)(C) of the act. See H. Rept. 98-857 Part 1, 98th Cong., 2d Sess. 23 (1984). In addition, for the purposes of 21 CFR 10.45, the agency is proposing, at 21 CFR 10.45(d), that a petition for reconsideration of a response to an ANDA suitability petition be submitted and acted upon before the agency's response will be considered final agency action.

The proposal retains the current regulations on the public availability of data and information in a petition. The availability of a petition for public examination and copying is governed by 21 CFR Part 20. Under those provisions, all data submitted in a petition, except data incorporated by reference, are available for public disclosure. The agency has on several occasions been asked to maintain confidentiality of petitions in which a petitioner seeks a determination of the suitability of an ANDA for a proposed drug product. Some petitioners oppose the public availability of such petitions on the ground that information contained in the petition may provide commercial advantage to competitors by, for example, disclosing a petitioner's marketing plans or new dosage form technology. The agency considered revising the regulations to provide for the confidentiality of any petition submitted under section 505(j)(2)(C) of the act until FDA has either approved or disapproved the petition, and if the agency disapproved a petition, to provide confidentiality for an additional 30 days to permit the petitioners to file a petition for reconsideration. The agency has initially rejected that position because it believes that the benefits in keeping the process a public one outweigh potential commercial problems to petitioners. In addition, data requiring confidentiality would ordinarily not need to be submitted in a petition under section 505(j)(2)(C) of the act. The public is specifically invited to comment on the alternative policy of nondisclosure of a petition submitted under section 505(j)(2)(C) of the act until final agency action on the petition. FDA does not anticipate that it will need to repropose this regulation if it ultimately adopts such a policy. Interested persons should prepare their comments accordingly.

D. Content and Format of an ANDA

The agency proposes to retain the current requirement that an applicant submit two copies of an ANDA, an archival copy, and a review copy. The agency will maintain guidelines under § 10.90(b) (21 CFR 10.90(b)) to help applicants comply with the content and format requirements of an ANDA.

1. *Archival copy.* Section 314.94 of the proposed rule describes the content and format requirements for ANDA's. In addition to the proposed requirements described below, the archival copy of an ANDA would contain, as now, the application form that contains the information described in § 314.50 (a) (1), (3), (4), and (5), a statement whether the submission is an abbreviated application under § 314.94 or a supplement under § 314.97 and a table of contents.

The proposed content requirements for an ANDA under § 314.94 (a) implement section 505(j)(2)(A) of the act. For a drug product that is the same as the reference listed drug, the ANDA procedures focus on the kinds of information necessary to assure that the duplicate product is the same as the reference listed drug and on the ability of the applicant to produce a drug product of acceptable quality. In these regulations, the term "same as" is used to describe drug products that are identical in specific key aspects (i.e., indications, dosage form, strength, route of administration, and active ingredient(s)), but allows certain appropriate differences due to different manufacturers (e.g., differences in inactive ingredients and certain labeling statements). (See discussion under Samples and labeling at part V section D.1.i.) A description of the proposed requirements for information to be included in an ANDA follows.

a. *Basis for ANDA submission.* The agency proposes in § 314.94(a)(3)(i) to require applicants to submit the name of the reference listed drug, including its dosage form and strength, that is the basis for the ANDA. In addition, for ANDA's submitted pursuant to an approved petition, proposed § 314.94(a)(3)(iii) would require reference to the petition by FDA assigned docket number and a copy of the agency's response to the petition stating that an ANDA may be submitted. (Section 505(j)(2)(C) of the act prohibits an applicant from submitting an ANDA for a drug product that differs from a listed drug in one of the active ingredients, route of administration, dosage form, or strength, unless FDA has approved a petition for the change.) Ordinarily both an ANDA and a petition submitted under section 505(j)(2)(C) of the act must refer to a single listed drug. However, as discussed above at part V section C., a petition may, under limited circumstances, rely on more than one listed drug. The agency's response to a petition permitting submission of an ANDA will identify the listed drug or drugs relied on for approval of the petition. The listed drug referred to in an ANDA for which a suitability petition was approved must be the same as the listed drug relied on in the petition.

Currently, the agency uses one product as a reference standard for bioequivalence determinations. Usually that reference standard is the pioneer drug product. Applicants will be required to refer and show bioequivalence to the listed drug selected by the agency as the standard for bioequivalence determinations. Therefore, where there is more than one listed drug for the same drug product, prospective applicants are encouraged to consult with the Director, Division of

Bioequivalence before selecting a reference listed drug.

Under FDA's DESI program, each **Federal Register** notice announcing the effectiveness conclusions reached in the DESI review about a drug product first approved for marketing before October 10, 1962, has included, when appropriate, an FDA finding that an ANDA is the suitable mechanism by which manufacturers or suppliers of duplicate versions of the first approved drug product could obtain FDA approval. Similar findings may, under the DESI or related programs, be made by the agency in the future. Where the agency has made such a finding and there is no other approved NDA or ANDA at the time of submission of an ANDA, the listed drug referred to in the ANDA would be the agency's notice published in the **Federal Register.** If the ANDA is for a duplicate of a drug product that is subject to FDA's DESI review and there is a listed drug, the applicant would refer to the listed drug as the basis for submission of the ANDA unless FDA has selected a different drug product as the standard for bioequivalence determinations.

The applicant must also include a statement as to whether the reference listed drug is entitled to a period of marketing exclusivity as provided under section 505(j)(4)(D) of the act. Exclusivity information on listed drugs is published in the list. If the listed drug is entitled to 5 years of exclusivity under section 505(j)(4)(D)(ii) of the act, ANDA's that refer to the drug may not be submitted until the exclusivity expires. All remaining periods of exclusivity accorded by sections 505(j)(4)(D)(i), (iii), (iv), and (v) of the act do not bar an applicant from submitting an ANDA. Such exclusivity does, however, require the agency to delay the effective date of approval of an ANDA.

b. *Conditions of use.* The agency proposes to require in § 314.94(a)(4) that the ANDA include sufficient information to show that the conditions of use, which include, among other things, indications and dosage instructions for which the applicant is seeking approval, have been previously approved for the reference listed drug. Except in extraordinary circumstances, an applicant would be expected to seek approval for all of the indications previously approved for the reference listed drug except for those indications that are protected by patent or that have been accorded periods of exclusivity. Consistent labeling for duplicate versions of a drug product, insofar as this is possible, will avoid differences that might confuse health care professionals who prescribe and dispense prescription drug products or might create omissions of significant information.

An applicant, however, may not seek approval in an ANDA or through an ANDA suitability petition for an indication that has not been previously approved. Approval of a new indication requires investigations to demonstrate the safety and effectiveness of the drug product for the new indication, and thus may not be obtained through an ANDA or suitability petition.

The requirement that the applicant show that its proposed conditions of use have been previously approved for the reference listed drug is satisfied if the applicant includes in the ANDA: (1) a statement that the conditions of use for which the applicant is seeking approval and for which the drug product will be marketed have previously been approved for the reference listed drug; and (2) reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug contained elsewhere in the ANDA.

c. *Active ingredients.* The agency proposes to require in § 314.94(a)(5) that the applicant provide sufficient information to show that the active ingredients of the drug product for which the applicant seeks approval are the same as those of the reference listed drug. The agency interprets the requirement that the active ingredients in the proposed drug product be the same as those of the listed drug to mean that the active ingredients must be identical. For example, if the proposed drug product contained a different salt or ester of the active ingredient in the listed drug, the active ingredient in the proposed drug product would not be identical to the active ingredient in the listed drug, and could not, therefore, be approved in an ANDA. Active ingredient in this context means the active ingredient in the finished drug product prior to its administration.

In some cases, an applicant may petition the agency to permit the applicant to vary an active ingredient in a proposed combination drug product. If the reference listed drug has one active ingredient, then the active ingredient in the applicant's drug product must be identical to that of the listed drug. See section 505(j)(2)(A)(ii)(I) and (j)(3)(C)(i) of the act. If the reference listed drug has more than one active ingredient, then all of the active ingredients in the applicant's drug product must be identical to those in the listed drug, except that an applicant may seek to vary one of the active ingredients of a listed combination drug product by the ANDA suitability petition procedure.

Under proposed § 314.94(a)(5), the requirement that the active ingredients in the applicant's drug product be shown to be the "same as" those of the reference listed drug is satisfied if the applicant includes in its ANDA: (1) A statement that the active ingredients in its product are the same as that of the reference listed drug except for any different active ingredient in a combination drug product that has been the subject of an approved petition and (2) reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug contained elsewhere in the ANDA.

For a combination drug product with an active ingredient different from that of the listed drug, the applicant would be required to provide information to show that (1) The different active ingredient is an active ingredient of another listed drug or of a drug which does not meet the definition of "new drug" in section 201(p) of the act and (2) the other active ingredients of the drug product are the same as those of the reference listed drug by referring to the applicant's annotated proposed labeling and the reference listed drug's approved labeling contained in the ANDA. The applicant would also be required to provide any other information about the different active ingredient that FDA may require.

d. *Route of administration, dosage form, and strength.* Under proposed § 314.94(a)(6), the applicant would be required to include in an ANDA sufficient information to show that the route of administration, the dosage form and the strength of the drug product for which the applicant is seeking approval are identical to those of the reference listed drug. An applicant may vary the route of administration, dosage form or strength of its product from the reference listed drug only if the applicant has petitioned FDA for permission to submit an ANDA for the differing drug product and the agency has approved the petition. An applicant satisfies the requirement to show that the route of administration, dosage form, and strength of its drug product are the same as those of the reference listed drug except for differences that have been the subject of an approved petition if the applicant includes in its ANDA: (1) a statement that the route of administration, dosage form, and strength are the same as those of the reference listed drug and (2) reference to the applicant's annotated proposed labeling and to the currently approved

labeling for the reference listed drug contained elsewhere in the ANDA. If the applicant has obtained permission to vary the route of administration, dosage form, or strength of the proposed product, the application must contain any information about the change as FDA may require.

e. *Bioequivalence.* The agency proposes at § 314.94(a)(7)(i) to require the applicant to include in an ANDA information sufficient to show that the drug product for which the applicant is seeking approval is bioequivalent to the reference listed drug. In addition, the proposed rule provides that for each in vivo study, an applicant include in the ANDA a description of the analytical and statistical methods used and a statement with respect to the applicant's compliance with the institutional review board regulations under 21 CFR Part 56 and the informed consent regulations under 21 CFR Part 50.

Under this proposal, the agency would retain, with one modification, the current definitions of the terms "bioequivalence" and "bioavailability" under Subpart A of 21 CFR Part 320. These terms are similarly characterized in section 505(j)(7)(A) and (B) of the act. The language of section 505(j)(7)(A) and (B) of the act is adopted except for a minor wording difference as noted below. Thus, a drug product for which an applicant is seeking approval in an ANDA would be considered bioequivalent to the reference listed drug if: (1) the rate and extent of absorption of the applicant's drug product do not show a significant difference from the rate and extent of absorption of the reference listed drug when administered at the same molar dose of the active moiety under similar experimental conditions in either a single dose or multiple doses or (2) the extent of absorption of the applicant's drug product does not show a significant difference from the extent of absorption of the reference listed drug when administered at the same molar dose of the active moiety under similar experimental conditions in either a single dose or multiple doses and the difference from the reference listed drug in the rate of absorption of the drug product is intentional, 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 product (21 CFR 320.1(e)). The second definition of bioequivalence in existing § 320.1(e) is similar to that proposed except that under the existing regulation a difference in rate of absorption must be: (1) Intentional and reflected in the labeling; (2) not essential to the attainment of effective body drug concentrations; or (3) considered medically insignificant for the particular drug. The language of section 505(j)(7)(B)(ii) of the act thus differs from the current regulatory definition in that a drug must now meet all three of the current criteria. FDA is proposing to adopt the statutory definition. (Also see part VI. Conforming Amendments.)

The second definition of the term bioequivalence may be applied, for example, in considering whether two controlled release products are bioequivalent. Therefore, for purposes of approval of an ANDA, if a controlled release dosage form of a drug product meets the four criteria in the second definition, it would be regarded as bioequivalent to the reference standard. However, for purposes of including the product in the list, FDA reserves the right to rate the product not "therapeutically equivalent" to any other listed drug containing the same active ingredient.

The term "bioavailability" means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product (21 CFR 320.1(a)). The agency proposes to expand this definition to include a reference to drugs that are not intended to be absorbed.

Currently, the agency uses one product as a reference standard against which the bioequivalence of the applicant's product is compared. The agency intends to continue that practice. Usually that reference product is the innovator's product, which would also usually be the listed drug referred to by the applicant. However, if the listed drug chosen by the applicant is different from that chosen by the agency as the standard for bioequivalence determinations, the agency will require the applicant to amend its application to refer to the agency's bioequivalence reference standard as its listed drug. This policy is intended to assure that all generic products remain equivalent to a common standard and thus to each other.

The agency notes that the statutory definitions of "bioavailability" (section 505(j)(7)(A) of the act) and "bioequivalence" (section 505(j)(7)(B) of the act) use the phrase "therapeutic ingredient" rather than the phrase "therapeutic moiety," which is used in 21 CFR Part 320. FDA does not believe Congress intended a meaning different from that in 21 CFR Part 320 for drug products that are the subject of ANDA's, because the legislative history of the 1984 Amendments, in discussing the terms "bioavailability" and "bioequivalence," refers to 21 CFR 320.1 (a) and (e). See H. Rept. 98-857 Part 1, 98th Cong., 2d Sess. at 31 (1984). The agency, however, believes that the term "active moiety" is more appropriate and proposes to substitute this term for the term "therapeutic moiety" or "therapeutic ingredient" in defining the terms "bioavailability" and "bioequivalence.

Both the statutory definition of "bioequivalence" and the definition under § 320.1(e) describe a standard for demonstrating in vivo bioequivalence for systemically absorbed drug products. Some drug products are not intended for systemic absorption, e.g., a topically applied drug product, an antacid or a radiopaque medium. Nevertheless, the statute imposes a bioequivalence requirement on all drug products for which an applicant is seeking approval in an ANDA. Where the usual in vivo bioequivalence methods (blood level measurements) are not applicable, suitable alternative methods, such as measurement of acute pharmacologic effect or demonstration of equivalent clinical effectiveness (with appropriate confidence intervals), may be established where FDA determines that they are capable of demonstrating bioequivalence. FDA notes, however, that where no methodology capable of establishing bioequivalence has been shown to exist for a particular drug or class of drugs, ANDA's for the drug cannot be approved until adequate methodology becomes available. (See section 505(j)(3)(F) of the act.)

In vitro dissolution may also be determined by the agency to be an appropriate means of demonstrating bioequivalence, for example, where an in vitro test has been correlated with human in vivo bioavailability data. The list specifies whether an in vitro or in vivo bioequivalence study will be required for ANDA's that refer to a listed drug. One method of demonstrating bioequivalence will generally apply to all indications for which the listed drug is approved, unless there is more than one route of administration in which case it may be necessary to study bioequivalence by more than one route. If any person believes that a specified method demonstrates bioequivalence only for a certain indication, that person may raise the issue with the agency. The agency will decide each such issue on a case-by-case basis.

Before enactment of the 1984 Amendments, the agency deferred or waived the requirement for the submission of evidence of in vivo bioavailability for various drugs for a

number of reasons. For example, FDA deferred the requirement if adequate methodology were not available for in vivo testing. However, section 505(j)(2)(A)(iv) of the act requires that the applicant provide information to show that its drug product is bioequivalent to the listed drug referred to by the applicant. Thus, there is no statutory provision for deferral of the requirement. Therefore, in those situations where methodology for in vivo testing is not available, the applicant is required to develop adequate methodology for such testing, or to carry out clinical studies to assess therapeutic equivalence, unless the agency determines that in vitro methods can be used to demonstrate bioequivalence.

In some cases, the in vivo bioavailability of a drug product may be self-evident, e.g., for a drug product that is a solution intended for intravenous or oral administration. The regulations under 21 CFR Part 320 set forth the criteria for waiver of evidence of in vivo bioavailability. (Also see discussion about proposed revisions to the waiver criteria under part VI.) The agency does not believe Congress intended that unnecessary human research be conducted in cases where an applicant could demonstrate that a product is inherently bioequivalent to another product and therefore meets the statutory standard of bioequivalence. Therefore, the agency proposes to continue its policy that if an applicant can demonstrate that its proposed drug product falls in this category, such a demonstration would be considered adequate information to show bioequivalence to the reference listed drug, as required in proposed § 314.94(a)(7)(i). Likewise, if the agency concludes that bioequivalence can be demonstrated by in vitro tests, the agency proposes to require only such tests rather than in vivo studies. (See section 505(j)(6)(A)(i)(III) of the act.) The agency informs prospective applicants of whether in vivo or only in vitro tests will be required through its list. In addition, the agency may from time to time, prepare or modify existing guidance documents for conducting bioequivalence studies. To assure that all applicants receive the most up-to-date version of any available guidance documents on the types of studies recommended for establishing bioequivalence, FDA publishes a complete listing of the most current available guidance documents in the list.

Many applicants now submit bioequivalence protocols to obtain agency review and comment before beginning bioequivalence tests. The agency proposes to continue to permit the submission of these protocols. An ANDA that contains a bioequivalence protocol and the chemistry, manufacturing, and controls data required by § 314.94(a)(9) would be considered sufficiently complete to start the statutory 180-day review period. However, an applicant certifying patent invalidity or noninfringement must submit completed bioequivalence studies with the initial ANDA submission (see section 505(j)(2)(B) of the act).

f. *Therapeutic effect.* Under the petition procedure, an applicant may seek to substitute one of the active ingredients in its proposed combination drug product for one of the active ingredients in the reference listed combination drug. If FDA approves a petition permitting the submission of an ANDA for such a change, the ANDA must contain information to show that the different active ingredient in the proposed drug product is of the same pharmacological or therapeutic class as the ingredient in the reference listed drug that was changed and that the proposed drug product can be expected to have the same therapeutic effect as the reference listed drug when administered to patients for the conditions of use approved for the listed drug and for which the applicant is seeking approval. (See section 505(j)(2)(A)(iv) of the act.)

With respect to the requirement that the substituted active ingredient be "of the same pharmacological or therapeutic class" as that of the listed drug, FDA would view the different active ingredient as being of the same pharmacological or therapeutic class as that of the listed drug if the applicant can show that the different active ingredient in its proposed drug product has similar pharmacologic properties to the ingredient in the listed drug that has been changed. FDA would view a drug product as being expected to have the same therapeutic effect as the listed drug if the applicant can demonstrate that: (1) 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. This will ordinarily require a showing that there is general acceptance in the scientific community that the specified doses of the two ingredients are equipotent; (2) the unchanged active ingredients in the applicant's drug product are bioequivalent to those in the reference listed drug; and (3) the different active ingredient in the applicant's drug product is bioequivalent to an approved dosage form of a drug product containing that ingredient and approved for the same indication(s) as the proposed 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. This would demonstrate that the different active ingredient is as bioavailable from the combination drug product as it is when separate preparations of the active ingredient are given. During its review of the ANDA, FDA may request the submission of additional information to show that the proposed drug product can be expected to have the same therapeutic effect as the listed drug.

g. *Chemistry, manufacturing, and controls.* The agency proposes at § 314.94(a)(9)(i) to retain the current requirement of the submission of adequate chemistry, manufacturing, and controls information described under § 314.50(d)(1). Current agency practice permits applicants to submit this information and bioequivalence protocols before beginning bioequivalence tests of their drug products and submitting the results of these tests to FDA. Thus, applicants are able to obtain agency review and comment on their formulation data, bioequivalence protocols, and pilot studies before conducting bioequivalence tests. The agency intends to continue this practice, except that ANDA's that contain a section 505(j)(2)(A)(vii)(IV) patent certification must submit completed bioequivalence studies with the initial ANDA submission.

h. *Inactive ingredients.* The inactive ingredients or composition used in a generic drug product must not raise serious safety questions. (See discussion in part V section M., *infra.*) The agency intends to place more stringent limitations on the variations permitted in the inactive ingredients in the formulation of parenteral, ophthalmic, and otic drug products than on other dosage forms. This is because each parenteral, ophthalmic, and otic drug product represents an individual pharmaceutical system with its own characteristics and requirements. In the formulation of parenteral drug products, certain added substances are used to maintain solubility, stability, sterility, and to increase patient comfort (i.e., by adjusting toxicity and reducing tissue irritation). Added substances selected

for parenteral drug products must be known to be of the highest quality, must be known to not interfere with the therapeutic effectiveness of the product and must be known to be nontoxic in the quantities used. The sensitivity of inactive ingredients in parenteral drug products is reflected in regulations under 21 CFR 201.100 which require that certain added substances and their concentrations be listed on the label of the product. Similarly, added substances are used in the formulation of products intended for ophthalmic and otic use such as buffers, antimicrobial preservatives, chemicals to adjust toxicity, and thickening agents.

Generally, in an ANDA, the formulation of ingredients in parental, ophthalmic, and otic dosage forms must be identical to the formulation of the reference listed drug identified in the ANDA. For the reasons described above, the agency will presume any inactive ingredient in an applicant's proposed drug product different from that in the reference listed drug to be unsafe unless the applicant can rebut the presumption by demonstrating that the different inactive ingredient will not affect the safety of its proposed drug product. Differences from the reference listed drug in the types of added substances described above for parenteral, ophthalmic, and otic dosage forms may be permitted if the applicant includes in its ANDA an identification and characterization of the differences in added substances between the proposed drug product and reference listed drug and demonstrates that such differences will not affect the safety of the proposed drug product.

For all dosage forms, the applicant would be required to identify and characterize any differences between the formulation of its proposed drug product and that of the reference listed drug and include in the ANDA information to show that the inactive ingredient will not adversely affect the drug product's safety.

1. *Samples and labeling.* The agency proposes at § 314.94(a)(10) to: (1) retain the current requirement under § 314.50(e) that upon FDA's request, the applicant submit samples of the finished drug product, the drug substances used in the manufacture of the drug product, and reference standards and blanks and (2) retain the current requirement under § 314.50(e) with respect to the submission of analytical methods and descriptive information needed to perform the tests on the samples and to validate the applicant's analytical methods.

The agency also proposes at § 314.94(a)(8)(ii) to retain the current requirement under § 314.50(e)(2)(ii) for the submission of copies of the proposed or final printed label and labeling for the drug product for which the applicant is seeking approval, i.e., four copies of draft labeling or 12 copies of final printed labeling.

The agency proposes to add a new requirement with respect to the submission of labeling. The statutory provisions of section 505(j) of the act require that an applicant provide sufficient information to assure that a generic version of a previously approved drug product is the same as the listed drug in dosage form, strength, and route of administration, contains the same active ingredients, except for differences from the listed drug that have been the subject of an approved petition, and generally is recommended for administration under the same conditions of use. In addition, the act requires that an applicant include in the ANDA information adequate to show that the proposed labelling for its drug product is the same as that of the reference listed drug except for changes required because of differences approved under a petition or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Thus, an applicant's proposed labeling might differ from that of the reference listed drug because: (1) the method of formulation (e.g., inactive ingredients) differs; (2) the applicant's product and the reference listed drug have different strengths (in the case of petition-approved drug products) or with respect to the "how supplied" section of the labeling, the generic manufacturer does not supply all strengths of the drug product; (3) the reference listed drug labeling does not reflect current agency labeling standards; for example, the agency may require a change in the labeling of a drug product to make available important new information about the safe use of a drug product, but the reference listed drug's labeling has not yet been updated to reflect this change; (4) the reference listed drug labeling includes conditions of use that are protected by a patent or are accorded a period of exclusive marketing; (5) the name and address of the manufacturers of the proposed and listed drug products vary; (6) the expiration dates for the proposed product and the reference listed drug differ; (7) the National Drug Code (NDC) number for the proposed product and the reference listed drug differ, if displayed on the label and in the labeling; and (8) there are differences in the color used in a tablet (e.g., the listed drug contains Yellow No. 5, which must be declared in the label, while the proposed product uses a different color).

FDA emphasizes that the exceptions to the requirement that a generic drug's labeling be the same as that of the listed drug are limited. The agency will not accept ANDA's for products with significant changes in labeling (such as new warnings or precautions) intended to address newly introduced safety or effectiveness problems not presented by the listed drug. Such labeling changes do not fall within the limited exceptions in sections 505(j)(2)(A)(v) and 505(j)(3)(G) of the act. Moreover, FDA does not believe that it would be consistent with the purpose of section 505(j) of the act, which is to assure the marketing of generic drugs that are as safe and effective as their brand-name counterparts, to interpret section 505(j)(2)(A)(v) of the act as permitting the marketing of generic drugs with diminished safety or effectiveness and concomitantly heightened labeled warnings. Thus, where a proposed change in a generic drug, e.g., in packaging or inactive ingredients or, for a petition-approved drug, in the approved change, would jeopardize the safe or effective use of the product so as to necessitate the addition of significant new labeled warnings, the proposed product would not satisfy the labeling requirements of sections 505(j)(2)(A)(v) and 505(j)(3)(G) of the act.

To assist the agency in determining if the applicant's proposed labeling is the "same as" that of the reference listed drug, except for the types of differences described above, FDA proposes in § 314.94(a)(8)(iv) to require the applicant to include in the ANDA a side-by-side comparison of the applicant's proposed labeling with the currently approved labeling for the listed drug referred to in the ANDA with all differences annotated and explained. Current approved labeling for any approved drug product may be obtained under 21 CFR Part 20 pursuant to the Freedom of Information Act. In addition, the proposed rule provides that an applicant must include in the ANDA a statement that the proposed labeling is the same as that of the listed drug except for those allowable differences specifically cited by the applicant. Where the agency has issued class labeling or another labeling standard, e.g., labeling requirements set forth in a DESI notice, and the applicant believes such labeling is more appropriate than the listed drug product's labeling, the applicant should refer to such labeling or standard and explain why it is more appropriate.

j. *Patent certification.* The statute prevents an ANDA from becoming

effective before all relevant listed product and use patents that have been filed for the listed drug have expired or, if the generic applicant asserts either that the generic product will not infringe the patent or that the patent is invalid, until the patent owner and listed drug holder have been notified and have had an opportunity to litigate the matter. Sections 505 (b) and (c) of the act require that applicants for all newly submitted or pending new drug applications and holders of all previously approved new drug applications submitted under section 505(b) of the act submit to FDA the patent number and the expiration date of any patent that claims the drug in the new drug application or that claims a method of using such drug with respect 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, sale, or use of the drug product.

The patents covered by the statutory provisions for submission of patent information are those that claim the drug product for which approval is being sought, including an active ingredient in such product and use patents that claim a particular indication or method of using the drug product. The agency interprets the statutory language "any patent which claims the drug" to include formulation and composition patents that claim the drug product for which approval is being sought. The 1984 Amendments do not authorize the submission of information for patents that claim a method of manufacturing a listed drug or that claim drug products for which the applicant is not seeking or has not obtained approval. FDA is required to publish the required patent information submitted under section 505 (b) or (c) of the act. The patent information appears in the list.

i. *Patents requiring a certification or statement.* Proposed § 314.94(a)(12), which implements sections 505(j)(2)(A)(vii) and (viii) of the act, requires applicants to include in their original ANDA submission a certification or statement as to each patent that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or a use of the reference listed drug for which the applicant seeks approval. A certification under § 314.94(a)(12)(i) or statement under § 314.94(a)(12)(iii), as appropriate, must be submitted whenever an applicant believes that the reference listed drug is claimed by an ingredient patent, drug product patent (including a formulation and composition patent), or a method of use patent. In some instances, an applicant may have to make multiple certifications if there is more than one relevant patent on the listed drug. For example, if the active ingredient patent for the listed drug has expired but a valid formulation patent will not expire for 3 years, then the applicant would be required to certify, for example, that one patent has expired and the other will expire in 3 years.

The patent information submitted to FDA, whether or not published in the list, should be the basis of the applicant's certification. To assist the applicant in determining whether information on a relevant patent has been submitted to FDA, the agency will place copies of new patent submissions on approved drug products and, prior to its publication, a copy of the patent information supplement to the list on public display in the Freedom of Information Office (HFI-35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857 Once a year, FDA conducts a review of the patent information published in the list and deletes all patents that have expired in the course of the year. Thus, an applicant should check the list for published patent information and FDA's Freedom of Information Office for patent information submitted to FDA but not yet published. FDA would also expect that an applicant would check the Patent Office for U.S. patents issued but not yet submitted to FDA. If the applicant is aware of a U.S. patent that claims the drug, drug product, or a method of using the drug that has been granted but not yet submitted to FDA, it must submit a certification under section 505(j)(2)(A)(vii)(I) of the act or, if applicable, a statement under section 505(j)(2)(a)(viii) of the act. If an applicant becomes aware, after submitting an ANDA, of a newly issued patent or if a patent is timely submitted after the submission of the ANDA, an appropriate new certification would be required in the form of an amendment to the pending ANDA.

ii. *Patent certifications or statement.* Under section 505(j)(2)(A)(vii)(I) of the act, an applicant must make a "paragraph I" certification if the applicant is aware, e.g., through a patent search, that a patent exists that claims the listed drug or that claims a use for such listed drug for which the applicant is seeking approval and for which patent information is required to be submitted, but for which the holder of the approved application for the listed drug has not submitted the information to FDA (proposed § 314.94(a)(12)(i)(A)(*1*)).

Under section 505(j)(2)(A)(vii)(II) of the act, an applicant must make a "paragraph II" certification if the applicant believes that there was a patent that claimed the listed drug or that claimed a use for such listed drug but that such patent has expired (proposed § 314.94(a)(12)(i)(A)(*2*)).

Under section 505(j)(2)(A)(vii)(III) of the act, an applicant must make a "paragraph III" certification if the applicant believes that there is an unexpired patent that claims the reference listed drug or that claims a use for such listed drug and the applicant does not want to certify that the patent is invalid or will not be infringed by the applicant's proposed drug product. The certification must state the date on which the patent will expire (proposed § 314.94(a)(12)(i)(A)(*3*)).

Under section 505(j)(2)(A)(vii)(IV) of the act, an applicant must make a "paragraph IV" certification if the applicant believes that there is a relevant unexpired patent that claims the listed drug or that claims a use for such listed drug, but also believes that the patent is invalid or will not be infringed by the applicant's proposed drug product. In addition, if the proposed drug product is a generic copy of a listed, patented drug and is the subject of a patent licensing agreement with the patent owner, the applicant would submit a paragraph IV certification. The agency proposes at § 314.94(a)(12)(i)(A)(*4*) that a paragraph IV certification be submitted to FDA in the following form:

I, (*name of applicant*), certify that Patent No. ——(*is invalid or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product*) for which this application is submitted.

The certification must be accompanied by the statement required by section 505(j)(2)(B)(i) of the act that the applicant will give the notice required by section 505(j)(2)(B)(ii) of the act and proposed § 314.95(a) to the patent owner or its representative and the holder of the approved application for the listed drug and by a statement that the applicant will comply with the requirements under proposed § 314.95(c) with respect to the content of the notice. A certification in any other form will not be accepted by the agency as a paragraph IV certification.

If, in the applicant's opinion and to the best of its knowledge, no relevant patents claim the listed drug or a method of using the listed drug, the agency proposes at § 314.94(a)(12)(ii) to require the applicant to include in its ANDA the following certification:

In the opinion and to the best knowledge of (*name of applicant*), there are no patents that

claim the listed drug referred to in this application or that claim a use of the listed drug.

This will assist the agency in assuring that each applicant has complied with section 505(j)(2)(A)(vii) of the act. If a patent is removed from the list after an applicant has submitted one of the certifications described in § 314.94(a)(12)(i)(A), and the application is pending or has a delayed effective date, the applicant should submit an amended certification under § 314.94(a)(12)(ii) certifying that there are no relevant patents. The new certification should be submitted either as an amendment to a pending application or by letter to an approved application.

If there is a patent claiming a method of using the listed drug, and the labeling for the applicant's proposed drug product does not include any indications that are covered by the use patent, proposed § 314.94(a)(12)(iii) would require the applicant to submit a statement that the method of use patent does not claim any of the proposed indications. The applicant should not submit a certification under § 314.94(a)(12)(i)(A) for such a patent. If, however, the labeling of the proposed drug product includes an indication that, according to the patent information submitted to FDA under sections 505 (b) and (c) of the act or in the opinion of the applicant, is claimed by the use patent, the applicant must submit an applicable certification under § 314.94(a)(12)(i)(A).

If patent information is submitted on a listed drug and, if, as of the time FDA concludes that an ANDA that refers to that drug is approvable, the ANDA applicant has not submitted an appropriate certification or statement on the patent, FDA will notify the applicant of the existence of the submitted patent before approval. (Because the applicant will then have to comply with any applicable certification and notification requirements, possibly delaying approval, applicants should make every effort to keep themselves informed as to whether patent information has been submitted while their ANDA's are pending.) If, however, a patent on the listed drug is issued by the Patent Office after an ANDA is submitted to FDA, and the holder of the approved application for the listed drug does not submit patent information within 30 days of issuance of the patent as required by section 505(c) of the act, the agency is proposing that no recertification be required for a pending ANDA that refers to that drug, if the ANDA applicant has previously submitted an appropriate certification. If the approved application holder ultimately submits the information late, the applicant need not submit an amended certification. A generic applicant whose application is submitted *after* a late submission of patent information on the listed drug or whose application is pending but does not contain a previously submitted certification, must, however, certify as to that patent. (See proposed § 314.94(a)(12)(vi) and discussion at part V section Q.4, *infra.*)

iii. *Patent licensing agreements.* The agency proposes in § 314.94(a)(12)(i)(B) and (v) to implement the following patent certification rules where the proposed drug product or the listed drug is a copy of a patented drug and is the subject of a patent licensing agreement with the patent owner. If the proposed drug product is a generic copy of a patented drug and the applicant has obtained a licensing agreement with the patent owner, FDA proposes to require the applicant to submit a certification under section 505(j)(2)(A)(vii)(IV) of the act. In response to the notice of certification from the generic applicant to the patent owner, the patent owner may consent to an immediate effective date of approval of the generic applicant's application by providing FDA with a written statement that the patent owner and the applicant have entered into a patent licensing agreement and consent to an immediate effective date. In such cases, i.e., when the agency is informed by the patent owner of a licensing agreement, the agency may, if all other requirements are met, approve the ANDA before the 45-day statutory period has elapsed. The written statement from the patent owner should be in the following form:

(*Name of patent owner*), owner of Patent No. _____, and (*name of applicant*) have entered into a patent licensing agreement that authorizes (*name of applicant*) to engage in the manufacture and sale of (*name of proposed drug product*). (*Name of patent owner*) does not object if FDA makes the approval of (*name of applicant's*) ANDA for (*name of proposed drug product*) effective at any time on or after the date of this statement.

If an ANDA refers to a listed drug that is itself a licensed generic version of a patented pioneer drug, the ANDA must include a certification as to any relevant patent on the pioneer drug. Section 505(j)(2)(A)(vii) of the act requires an applicant to make a certification "* *with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval* under [section 505(j)] and for which information is required to be filed under subsection (b) or (c) *" (emphasis added). Because, where a licensing agreement is necessary, the patent will claim both the pioneer drug product and generic copies of that drug product, an ANDA that refers to the licensed copy must include a certification as to any patent on the pioneer for which information was required to be filed under section 505 (b) or (c) of the act. When the agency is aware of a patent licensing agreement between the applicant of a listed generic drug and a patent owner, it will publish in the list information on the patent next to the listing for the licensed generic drug.

iv. *Amended certifications.* FDA is proposing to require an applicant who has made a paragraph IV certification to amend its patent certification if the applicant has a pending ANDA or an ANDA with a delayed effective date and one of the following occurs: (1) a final judgment is entered finding that the applicant's product infringes the patent, or (2) the patent is removed from the list for any reason other than because the patent has been declared invalid in a lawsuit brought by the patent owner within 45 days of the receipt of notice under section 505(j)(2)(B) of the act. Once amended, the application will not be considered to be one containing a paragraph IV certification for purposes of section 505(j)(4)(B)(iv) of the act.

A patent certification must also be amended if the applicant learns that its previous certification is incorrect, with two exceptions. First, as described above in part V section D.1.j.ii., an applicant who has made an appropriate certification would not be required to amend the certification if, following the first certification, the listed drug applicant submits information on a patent on the listed drug, but the submission is untimely.

Second, FDA is proposing not to require an amended certification if after an ANDA is approved, whether or not the approval is effective, the listed drug applicant submits information on a patent on the listed drug, whether the submission is timely or not. Once an ANDA becomes effective, new patents issued on a listed drug are not subject to the patent certification provisions of the 1984 Amendments; the patent holder may enforce such a patent under the patent provisions of Title 35 of the United States Code, but is not entitled to notice from the ANDA applicant or to a period during which the ANDA applicant is kept off the market while the patent issue is litigated. Any delay in an ANDA's effective date will be entirely unrelated to the timing of the issuance of a new patent on the listed

drug. Accordingly, FDA believes that requiring an amended certification if a patent is issued after approval of an ANDA but before its effective date would provide an unintended windfall to the listed drug applicant, who, but for the fortuitous delay in the ANDA's effective date, would not have reaped the benefits of the patent certification provisions of the 1984 Amendments. However, FDA specifically seeks comment on whether an amended certification should be required under these circumstances, and on the policies, if any, that would be served by requiring such an amendment.

2. *Review copy.* The agency proposes to retain the current requirement that, in addition to the complete archival copy, an applicant submit a review copy of an ANDA that contains two separately bound sections. One section would be required to contain a copy of the application form, the chemistry, manufacturing, and controls information described in proposed § 314.94(a)(9), the information described in proposed § 314.94(a)(3) (basis for ANDA submission), § 314.94(a) (4) through (6), (8), and (12), 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 will contain a copy of the application form, the information described in § 314.94(a)(3) (basis for ANDA submission) and (7) (bioequivalence information) and a copy of the currently approved labeling for the reference listed drug and of the applicant's annotated proposed labeling.

E. Notice of Certification of Invalidity or Noninfringment of a Patent

Proposed § 314.95 incorporates the requirements of section 505(j)(2)(B) of the act with respect to notification of the patent owner and the holder of the approved application for the listed drug when an applicant certifies under section 505(j)(2)(A)(vii)(IV) of the act that a patent is invalid or will not be infringed. In addition, proposed § 314.95 describes the information to be included in the notice.

The act permits an applicant who wishes to market a generic version of a listed drug product to challenge a drug or use patent that the pioneer application holder identifies as precluding the marketing of the generic version. An applicant who submits an ANDA to FDA for the generic version of the listed drug and wishes to initiate such a challenge must certify that the relevant patent submitted by the pioneer application holder to the agency is invalid or will not be infringed. The applicant must then give notice of its certification to (1) the owner(s) of each relevant patent or the representative designated by the patent owner to receive such notice and (2) the holder of the approved application under section 505(b) of the act for the reference listed drug claimed by the patent or the holder's representative (attorney, agent, or other authorized official).

Under the proposal, an applicant is required to provide the notice of certification when it receives FDA's acknowledgment of the receipt of an ANDA that is acceptable for review. Although the legislative history states that Congress intended that the notice be sent simultaneously with submission to FDA of the ANDA, the statute requires the applicant to state in the notice that an application "has been submitted. Moreover, the statute requires the notice to state that the application contains data from bioavailability or bioequivalence studies. Receipt of the notice by the patent owner or its representative or the approved application holder triggers the start of the 45-day clock within which a patent owner or application holder must bring suit if it wishes to challenge an applicant's certification of patent invalidity or noninfringement. The statute and legislative history of Title I demonstrate that Congress did not intend incomplete application submissions to trigger legal action by a patent owner or approved application holder.

The agency therefore proposes that the notice be sent only upon submission of a "complete" application. An applicant must first submit an ANDA and certify in the application that it will provide the required notice to the patent owner or its representative and to the pioneer application holder. After receipt of the application, the agency will determine if the application is acceptable for review. An application containing a paragraph IV certification that does not contain the results of any required completed bioavailability or bioequivalence studies that meets an appropriate FDA guidance or that is reasonable in design, and that purports to show that the proposed drug is bioequivalent to the listed drug, would not be considered acceptable for review. Neither a protocol nor a pilot study will be considered acceptable. If, however, the ANDA is for a drug for which a bioequivalence study is not required, e.g., a parenteral product, the application may be considered acceptable for review if it contains a waiver of a bioequivalence study requirement. If the application is acceptable for review, FDA will notify the applicant in writing and provide the applicant with the ANDA number assigned by FDA. Immediately upon receipt by the applicant of FDA's acknowledgement letter, the applicant would be required to notify the persons described in the statute of the certification of invalidity or noninfringement, and amend the ANDA to include a statement certifying that the notice has been provided and that the notice contains the required information, described at § 314.95(c). If an abbreviated application is amended to include a paragraph IV certification because the applicant learns of a relevant patent after the abbreviated application is submitted and before its approval, the applicant would be required to notify the appropriate parties when the amendment is submitted to FDA. If a patent on a listed drug is issued after an abbreviated application is approved, the generic applicant need take no further action.

The agency does not propose to require the applicant to notify holders of approved applications for drugs other than the listed drug claimed by the product or use patent. If an ANDA refers to a licensed generic version of a patented pioneer drug and the applicant made a certification as to the patent on the pioneer drug, the applicant must notify the patent owner and the holder of the approved pioneer application of its certification.

An applicant may obtain the name and address of the patent owner or the attorney or agent designated to represent the patent owner in patent proceedings (attorney or agent of record) from the United States Patent and Trademark Office. The name and address of the holder of the approved application or the holder's attorney, agent, or authorized official (i.e., the person who signed the Form FDA 356h) may be obtained from FDA's Center for Drug Evaluation and Research, Division of Drug Information Resources (HFD-80).

The 45-day clock would start on the first day after the date of receipt of the notice by the patent owner or its representative or by the approved application holder if it is an exclusive patent licensee as documented by the applicant under proposed § 314.95(e). Although an applicant is required to provide the notice to the patent owner and approved application holder, FDA believes it is appropriate to rely solely on the patent owner to make decisions about bringing patent infringement actions, unless there is a patent license

agreement and the approved application holder is the exclusive patent licensee. In the latter situation, FDA would expect the exclusive licensee to bring suit for patent infringement. Therefore, the date of receipt of the notice by an application holder who is not an exclusive licensee for the patent will not trigger the start of the 45-day clock. The agency specifically seeks comment on this policy.

FDA will accept as adequate documentation of the date of receipt of the notice (1) a return receipt or (2) a letter acknowledging receipt from the patent owner and approved application holder. If an applicant wishes to rely on another form of documentation, the applicant should first check with the agency. The applicant would be required to amend the ANDA to include a copy of the return receipt or other such evidence of the date the notification was received by the patent owner and approved application holder.

Proposed § 314.95(c) lists the information to be included in the notice. Under the proposal, the notice would cite section 505(j)(2)(B)(ii) of the act as the relevant statutory authority for the notice and contain: (1) a statement that FDA has received an ANDA submitted by the applicant containing any required bioavailability or bioequivalence data or information, (2) the ANDA number assigned by FDA, (3) the established name, if any, of the drug product that is the subject of the ANDA, (4) the active ingredient, strength, and dosage form of the proposed drug product, (5) the patent number and expiration date, as submitted to the agency or as known to the applicant, of each patent alleged to be invalid or not infringed, (6) a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed, and (7) if the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant. With respect to the factual and legal basis for the applicant's certification, the agency proposes that for each claim of a patent noninfringement, the notice would be required to include an explanation of the alleged noninfringement. In addition, for formulation or composition patents, the notice would be required to include a description of a mechanism through which the applicant agrees to make the formulation or composition of the proposed drug product known to the patent owner or to a designated intermediary who will act as a referee. The agency believes that only by making the formulation or composition available to the patent owner or a designated third party will the patent owner have sufficient information to make an informed decision whether to sue for patent infringement. For each claim of patent invalidity, the notice would be required to include an explanation of the grounds supporting the allegation, including all statutory bases, affirmative defenses, reasoning, and evidence supporting the allegation, citing any relevant case precedent upon which the allegation is based, providing a copy of any patent or publication relied upon, and indicating that portion of each such patent or publication that is alleged to invalidate such claim and the reasons supporting such allegation.

Although the proposed regulations describe the information required by statute that an applicant must include in a notice, the applicant is not required to include a copy of the notice in its ANDA as suggested by the Pharmaceutical Manufacturers Association (PMA) (comments filed under Docket No. 85N-0214). Only a statement that such notice has been given by the applicant is required (21 U.S.C. 355(j)(2)(B)(i)). Determinations concerning the scope of patents are the province of the United States Patent and Trademark Office and of the courts. FDA does not have the expertise, nor is it required to review the notice as suggested by PMA. FDA proposes only to ensure that such notice has been sent and received. If the applicant meets the requirements under proposed § 314.95, which FDA believes will assure adequate notice, the agency will presume the notice to be complete and sufficient. Thus, the agency does not intend to intervene in cases where the patent owner or exclusive patent licensee claims that the notice was deficient. However, in cases where the notice was deemed inadequate by the patent owner or exclusive patent licensee and where the ANDA applicant subsequently amends the notice, the agency may, if the applicant amends its ANDA with a written statement that the date of receipt of the amended notification should be considered the date of receipt of notice, use the date of the amended notification to begin the 45-day statutory period for institution of an action for patent infringement.

F Amendments to an Unapproved ANDA

The agency proposes to revise its regulations regarding amendments to pending ANDA's.

Proposed § 314.96 would provide for extensions to the 180-day review clock under section 505(j)(4)(A) of the act only for evaluating major amendments (i.e., those requiring substantial FDA review time). Examples of such major amendments would involve amendments that contain data from a new bioequivalence study or stability or sterility study resulting from a drug product reformulation or change in the manufacturing or controls procedures, significant updated data from a change in the source of the drug substance or change in manufacturing facility, or data from a bioequivalence study where only a protocol was contained in the original submission. The agency would consider such an amendment, whether submitted on the applicant's own initiative or at the request of the agency, to constitute an agreement by FDA and the applicant to an extension of the review period under section 505(j)(4)(A) of the act. Any extension would start with the date of receipt by FDA of the amendment and would be limited to the time necessary for FDA to review the submission.

Under the proposal, an amendment that contains data and information to resolve substantial deficiencies in the ANDA as set forth in a not approvable letter under § 314.120 would extend the review period for 120 days from the date of receipt by FDA of the amendment. Although the agency now attempts to review these amendments quickly, the agency believes this is a reasonable period for review of an amendment to resolve substantial deficiencies and that establishing a uniform length of time for this review will eliminate the need to notify each applicant of the amount of time needed to review its amendment.

G. Other Applicant Responsibilities

1. *General.* The agency proposes to retain the current requirements for applicants under 21 CFR Part 314 regarding: (1) withdrawal by an applicant of an unapproved ANDA, (2) submission of supplements and other changes to an approved ANDA, (3) change in ownership of an ANDA, (4) submission of postmarketing reports, other than adverse drug experience reports, and (5) request for waiver of submission requirements.

2. *Postmarketing reports.* With respect to the requirements set forth under § 314.80 for reporting adverse drug experiences, the agency proposes in § 314.98 to require an applicant of an approved ANDA to comply with those requirements but only if the approval is effective under § 314.107 The objective of the adverse drug experience reporting requirements is to signal potential serious safety problems with marketed drugs, especially newly marketed drugs. An applicant cannot market a drug product before it has an effective

approval for its ANDA, so it is unlikely that the applicant, before this effective approval, would receive adverse drug experience information about other drug products through literature reports or unpublished scientific papers that would not also be received by the marketers of those drug products.

FDA is also proposing in § 314.98 the following changes in its adverse drug experience reporting requirements for applicants of ANDA's and abbreviated antibiotic applications. First, ANDA and abbreviated antibiotic application applicants would no longer be required to submit duplicate copies of adverse drug experience reports. This change is made possible by the centralization of FDA's processing of drug experience reports on generic versions of approved drug products in a single office in the Center for Drug Evaluation and Research that has the responsibility for ensuring the proper distribution and analysis of these reports. Ordinarily, the Division of Generic Drugs will not evaluate these reports and therefore no longer needs to receive a copy. Applicants should send one copy of each adverse drug experience report directly to the Division of Epidemiology and Surveillance (HFD–730).

Second, the proposed regulations would provide that an ANDA and abbreviated antibiotic application applicant submit to FDA periodic reports of adverse drug experiences only if (1) the applicant has received during the periodic reporting cycle adverse drug experiences not previously reported or (2) there are labeling changes initiated by the applicant.

FDA is also proposing the following revisions to § 314.80. First, the agency proposes to revise the definition of the term "adverse drug experience" by deleting the word "significant" in the phrase "any significant failure of expected pharmacological action. The word "significant" has been a source of confusion and ambiguity. FDA considers any report of failure of a drug to produce the expected pharmacological action to be significant. This proposed revision would unambiguously require that all reports of a therapeutic failure (lack of effect) be submitted to FDA. Second, the agency proposes to add the following new adverse drug experience reporting requirement. Under the proposal, applicants of both full and abbreviated applications would be required to review periodically (at least as often as the periodic reporting cycle) the frequency of reports of failure of a drug to produce the expected pharmacological action (lack of effect) received by an applicant and report any significant increase in frequency of therapeutic failure (lack of effect) to FDA within 15 working days of determining that an increase in frequency exists. Determinations of significant increases in frequency are to be based on FDA's "Guideline for Postmarket Reporting of Adverse Drug Reactions. Applicants would be required to submit these reports in narrative form (including the time period on which the increased frequency is based, the method of analysis, and the interpretation of results). These narrative reports would be required to be submitted under separate cover and not in a periodic report except for summary purposes. The intent of this proposed revision is to facilitate the identification of possible therapeutic failures with both generic and brand-name drug products, and to obtain evidence to confirm or refute reports of therapeutic inequivalence between generic drugs and their brand-name counterparts. (Also see part VI. Conforming Amendments.)

The agency proposes to retain the current requirement for the submission of other postmarketing reports under § 314.81, if applicable, upon approval of an ANDA, whether or not the approval is effective. For example, certain manufacturing and control changes not requiring a supplemental application under § 314.70(b) and (c) must be reported in an annual report, and advertising and promotional material must be submitted to FDA at the time of initial dissemination or initial publication.

3. *Waivers.* The agency proposes to retain the current requirement under § 314.90 under which an applicant may obtain a waiver of requirements for the submission of information in an application. The applicable sections are those set forth under new proposed Subpart C. FDA may not, however, waive statutory requirements.

H. Time Frames for FDA Actions on ANDA's

The agency proposes to revise its regulations regarding agency actions in receiving, reviewing, and approving or refusing to approve ANDA's to implement the provisions of section 505(j) of the act.

1. *Receiving and reviewing ANDA's.* Under section 505(j)(4)(A) of the act, within 180 days of the initial receipt of an ANDA, FDA must either approve or refuse to approve the ANDA, unless FDA and the applicant agree to an extension. If FDA refuses to approve the ANDA, it must give the applicant a notice of an opportunity for a hearing (NOOH) on whether the ANDA is approvable and will issue such a notice if the applicant elects to request a hearing rather than to amend or withdraw its application, see § 314.120.

Although the statute mentions "filing" an ANDA, filing does not trigger the statutory time period in which FDA must either approve or disapprove the ANDA. For an ANDA submitted to FDA under section 505(j) of the act, it is the time between the initial receipt of the ANDA and approval or disapproval. This differs from an application submitted under section 505(b) of the act, for which, within 180 days after filing an application, FDA must either approve the application or give the applicant a notice of opportunity for a hearing on whether the application is approvable, unless FDA and the applicant agree to an extension of time. For applications submitted under section 505(j) of the act, the agency considers the date of initial receipt of an ANDA to be the date FDA receives a submission that, on its face, is sufficiently complete to permit a substantive review. Such an ANDA may contain only the chemistry, manufacturing, and controls information required by § 314.94(a)(9) and a bioequivalence protocol unless the applicant certifies that a relevant patent is invalid or will not be infringed. In the latter case, the ANDA must contain also the results of any required bioequivalence studies.

Accordingly, the agency proposes revisions to § 314.101 to add the requirements for receipt of an ANDA. ANDA's will be reviewed for completeness when they are submitted. If an ANDA is not sufficiently complete to permit a substantive review, the applicant will be notified, normally by telephone. The applicant may then withdraw the application, amend the application to correct deficiencies, or take no action. FDA may elect to allow a deficiency to be corrected without a formal withdrawal of the ANDA and resubmission. If the applicant does not correct the deficiency, FDA will not consider the ANDA "received. If an ANDA is sufficiently complete to permit a substantive review, the application will be "received" and reviewed. (See proposed § 314.101(b).)

To clarify its applicability, the agency also proposes to revise the provision under § 314.101(e)(1) under which FDA will refuse to file an application if the drug product that is the subject of the submission is already covered by an approved application. The provision is intended to permit FDA to refuse to review spurious applications. For example, persons or firms who are

merely distributors of an already approved drug product do not need an approved application for the products they distribute. Therefore, the agency proposes to revise the provision to read, "The drug product that is the subject of the submission is already covered by an approved application and the applicant of the submission is merely a distributor and/or a repackager of the already approved drug product. The agency specifically seeks comment on whether there are appropriate exceptions or additions to this provision that should be expressly noted in the provision, e.g., for joint developers of a drug product, or distributors who engage in activities beyond that of a distributor because of a special relationship to the developer of the drug product.

2. *Approval of ANDA's.* Section 505(j)(3) of the act requires FDA to approve an ANDA if it finds that none of the statutory grounds for disapproval of the ANDA apply. The agency proposes to revise § 314.105 to state this requirement. Under the proposed revision, if FDA finds that none of the grounds in the statute for disapproval of an ANDA applies, the agency would approve the ANDA and send the applicant an approval letter. If only minor deficiencies exist in the applicant's draft labeling or if the applicant has not submitted final printed labeling to FDA and the application is otherwise approvable, FDA will send the applicant an approvable letter. The approvable letter will describe the information or material FDA requires and state a time period within which the applicant must respond. Unless the applicant corrects the deficiencies by amendment or submits final printed labeling within the specified time period, the agency would formally refuse to approve the application. The agency proposes to revise § 314.110 by adding a new paragraph (b) to state when FDA will send the applicant an approvable letter.

I. Applications Described by Section 505(b)(2) of the Act

Since 1977 FDA has permitted applicants who want to market generic copies of new drugs first approved after 1962 to file new drug applications that meet the "full reports" requirement of section 505 of the act with published reports in the medical literature establishing the generic drug's safety and effectiveness. FDA's policy of permitting approval of generic copies of approved drugs based on literature reports is commonly referred to as the "paper NDA policy," a complete description of which appears in the Federal Register of May 19, 1981 (46 FR 27396). The "paper NDA policy" applied only to duplicate drug products of post-1962 drugs, i.e., drug products which contained an active ingredient identical to an already marketed drug product first approved for marketing after 1962 in the same or closely related dosage form, and offered for the same indications as those of the already marketed drug product.

A paper NDA was a new drug application for a duplicate drug product submitted under section 505(b) of the act that satisfied the statutory criteria for a full application except that the full reports of investigations required by section 505(b) of the act to prove safety and effectiveness consisted entirely of references from the medical literature. A paper NDA differed from an abbreviated new drug application in that, in an abbreviated application, studies of safety and effectiveness (other than bioavailability) were not required to be submitted or identified by the applicant.

The 1984 Amendments to the act include provisions applicable to applications submitted under section 505(b)(1) of the act similar to those previously denominated paper NDA's. These new provisions, under sections 505(b)(2) and 505(c)(3) (D) of the act, describe an application submitted under section 505(b)(1) in which the investigations described in clause (A) of section 505(b)(1) 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. The requirement in clause (A) to which this provision refers mandates submission of "* full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use. Section 505(b)(2) of the act is significant because newdrug applications that contain full reports of investigations that were not conducted by or for the applicant or for which the applicant has not obtained a right of reference are subject to the patent certification and exclusivity provisions of the act. (See part V sections K. and L.)

Despite certain similarities between section 505(b)(2) of the act and the "paper NDA policy," the new statutory provision is broader than the paper NDA policy. Although the legislative history of the 1984 Amendments refers to "paper NDA's" in discussing the applications described in sections 505(b)(2) and 505(c)(3)(D) of the act, the language of these provisions does not limit the applications described to duplicates of already approved products. Instead, sections 505(b)(2) and 505(c)(3)(D) of the act, by their terms, apply to any application that relies on investigations which the applicant has not conducted, sponsored, or obtained a right of reference to, regardless of the similarity or dissimilarity of the drug product to an already approved drug product.

The agency therefore proposes, in accordance with the plain language of the statute, to interpret sections 505(b)(2) and 505(c)(3)(D) of the act to cover any application in which one or more of the investigations without which the application could not be approved, as described below, were not conducted or sponsored by the applicant or to which the applicant does not have a right of reference. Such applications may be for variations of approved drug products, or, rarely, for new chemical entities. (An application, however, for a new chemical entity would not be subject to any patent protection or exclusivity accorded a previously approved drug, because, by definition, there will be no applicable previously approved drug.)

Because the 1984 Amendments established a statutory scheme for the approval of all applications that, before the Amendments, would have been approved under the paper NDA policy, the agency believes that the policy is no longer necessary. For this reason, and to avoid confusion caused by the differences between the coverage of the paper NDA policy and the 1984 Amendments, FDA is hereby revoking the policy. FDA proposes to revise § 314.50 to delete the term "paper NDA wherever it now appears.

The agency does not, however, propose to treat all applications previously covered by the paper NDA policy as 505(b)(2) applications. Applications for duplicates of listed drugs eligible for approval under ANDA's will be treated as submitted under section 505(j) of the act rather than under section 505(b) of the act, even if such applications are supported by literature reports of safety and effectiveness. The agency intends to treat any application for a duplicate of a listed drug eligible for approval under an ANDA as an application under section 505(j) of the act because it believes that Congress intended the ANDA provisions to, among other things, assist the agency in avoiding duplicative reviews of safety and effectiveness information about already approved drugs. It would be inconsistent with this purpose to require FDA to

review safety and effectiveness information in 505(b)(2) applications when the statute also authorizes an abbreviated review under section 505(j) of the act. Moreover, because the patent certification and exclusivity provisions apply equally to applications described under section 505(b)(2) or 505(j) of the act, an applicant will not be disadvantaged by the review of its application under section 505(j) of the act rather than 505(b)(2) of the act.

The agency has considered expanding this policy to include applications for drug products that are modified versions of previously approved products, where the types of changes are those for which a section 505(j)(2)(C) petition could be approved permitting submission of an ANDA. As described above in part V section C., certain types of changes from an approved product, i.e., changes in dosage form, strength, route of administration and active ingredients, can be reviewed in a 505(j) application, if a petition under section 505(j)(2)(C) of the act is approved permitting the submission of an ANDA. Currently, an applicant can submit a 505(b)(2) application for a drug product with any of these types of changes rather than request permission to submit an ANDA through a 505(j)(2)(C) petition. Under an expanded policy, one option would be to treat a 505(b)(2) application for these types of changes as a 505(j)(2)(C) petition. Another option would be to return the 505(b)(2) application to the applicant and request the submission of a 505(j)(2)(C) petition. This expanded policy would also further assist the agency in avoiding reviews of safety and effectiveness information in a 505(b)(2) application for drug products for which the statute authorizes an abbreviated review under section 505(j) of the act. The agency specifically seeks comment on whether FDA should adopt such an expanded policy.

Applications described by sections 505(b)(2) and 505(c)(3)(D) of the act may therefore currently be submitted for: (1) drug products that could not be approved under section 505(j) of the act and (2) drug products with changes from an approved product that could be reviewed in an ANDA submitted pursuant to a 505(j)(2)(C) petition for which the applicant chose to submit a 505(b)(2) application rather than a petition. In practice, with respect to the first category of drug products, this means that 505(b)(2) applications will generally be submitted for never before approved changes in already approved drug products, where the change cannot be reviewed under section 505(j). As described above in part V section C., certain types of changes from an approved product, in dosage form, strength, route of administration and active ingredients, can be reviewed in a 505(j) application, as long as investigations are not necessary to evaluate the safety and effectiveness of the changed product. If such investigations are necessary, they can be reviewed only under the procedures applicable to 505(b) applications. Therefore, a 505(b)(2) application will be appropriately submitted for a drug product where the safety and effectiveness of the change must be, at least in part, established by investigations. Examples of such cases would be applications seeking approval of significantly different dosage forms or of new uses of already approved drugs. If it is necessary for FDA to review the results of investigations to approve the drug, but the applicant has not conducted, sponsored, or obtained a right of reference to one or more of the investigations necessary for approval of the application, the application will be treated as a 505(b)(2) application.

In addition to applications supported by literature reports or a combination of literature reports and new clinical investigations, FDA is proposing to treat as a 505(b)(2) application an application for a change in an already approved drug supported by a combination of literature or new clinical investigations and the agency's finding that a previously approved drug is safe and effective. (See part V section J., *infra.*)

The agency proposes to interpret the phrase "right of reference or use" as a right of reference to, or use of, the underlying raw data which provide the basis for the reports of investigations submitted in a 505(b)(2) application. Proposed revised § 314.3(b) incorporates this interpretation as the definition of the term "right of reference or use. A right of reference or use must be granted by the owner of the raw data. If the raw data are in the public domain, e.g., because they were developed in a publicly funded study, no express right of reference is necessary. FDA is proposing, under revised § 314.50(g), to require an applicant that has obtained a right of reference to, or use of, such raw data, to include in its application a written statement signed by the owner of the data that authorizes the applicant to use, in support of its submission to FDA, the raw data that provide the basis for each report of an investigation submitted in its application. Thus, the applicant must be able physically to make available the raw data for FDA audit, if necessary, or the data must be available for review by FDA in another application to which the applicant has a right of reference.

FDA proposes to interpret the phrase "investigations described in clause (A) and relied upon for approval" in sections 505(b)(2) and 505(c)(3)(D) of the act to mean any investigations without which the application could not be approved. Accordingly, an application is described by section 505(b)(2) of the act if the applicant has not conducted or sponsored or obtained a right of reference to every safety or effectiveness investigation without which the drug could not be approved. An application that contains one study conducted by the applicant but that relies on literature citations for the remainder of the safety and effectiveness data without rights of reference is thus considered an application described by section 505(b)(2) of the act.

In light of this interpretation, an applicant seeking to submit a so-called "full NDA and thereby avoid any exclusivity or patent rights attaching to a pioneer drug must conduct or sponsor the adequate and well-controlled investigations necessary to establish the effectiveness of the drug, or, if the applicant relies on literature for these studies, must obtain rights of reference to the data. The applicant must conduct, sponsor, or obtain rights of reference to these studies even if the pioneer applicant relied on literature citations. Similarly, the applicant must conduct, sponsor, or obtain a right of reference to all the safety tests without which the application could not be approved. In general, such tests will include animal carcinogenicity and reproduction studies, certain animal toxicity studies, and some clinical investigations. When a drug product has 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 described. Appropriate reliance on an analysis of these adverse reaction reports will not cause the application to be one described by section 505(b)(2) or 505(c)(3)(D) of the act.

This interpretation is consistent with Congress' intent to encourage the pharmaceutical industry to develop and seek approval of significant new therapies by conferring periods of exclusive marketing. If exclusivity could easily be avoided by an application containing only minimal data generated or purchased by the applicant, the incentive created by the availability of such exclusivity would decrease considerably.

The term "application" as defined in § 314.3 means both a full application submitted under section 505(b)(1) of the act that contains full reports of investigations conducted or sponsored by the applicant or for which the applicant has obtained a right of reference or use and an application submitted under section 505(b)(1) of the act that meets the description in section 505(b)(2) of the act, i.e., one or more of the investigations without which the application could not be approved relied on by the applicant for approval of the application were not conducted by or for the applicant and the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

Applications that meet the description in section 505(b)(2) of the act have been (under the "paper NDA policy"), and will continue to be, submitted under section 505(b)(1) of the act. They are therefore subject to the same statutory provisions that govern full new drug applications, except, of course, that the applicant has not conducted, sponsored, or obtained a right of reference to one or more of the investigations necessary to demonstrate safety and effectiveness. Thus, for example, 505(b)(2) applications may be entitled to periods of exclusivity and should submit any relevant information required under proposed § 314.50(j), and any relevant patent information required under § 314.53.

A new drug application that meets the statutory description in sections 505(b)(2) and 505(c)(3) of the act must satisfy patent certification requirements and is subject to any exclusivity accorded a relevant previously approved drug. The patent and exclusivity provisions applicable to 505(b)(2) applications are generally the same as those that apply to abbreviated new drug applications.

An applicant submitting a section 505(b)(2) application must make the same certifications with respect to patents as an applicant submitting an ANDA. (See part V section D.1.j., *supra.*) A 505(b)(2) applicant must make certifications with respect to each patent which, in the opinion of the applicant and to the best of its knowledge, claims the drug or drugs on which investigations that are relied upon by the applicant for approval of its application were conducted, or which claims a use for such drug or drugs. With respect to a use patent, if the labeling of the applicant's proposed drug product includes an indication that, according to the patent information submitted to FDA or in the opinion of the applicant, is claimed by the use patent, the applicant must submit to FDA an appropriate certification under section 505(b)(2)(A) of the act. If, however, there is a patent on a method of using the drug that was the subject of an investigation relies on in the application and the labeling for the applicant's proposed drug product does not include the indications that are covered by the use patent, the applicant must submit a statement under section 505(b)(2)(B) of the act that the method of use patent does not claim any of the proposed indications. As with ANDA's, if the applicant certifies that a patent is invalid or will not be infringed, the applicant is required to give notice to patent owners and holders of approved new drug applications. Applicants who have licensing agreements with patent owners will also be required to follow the same rules as licensed ANDA applicants. FDA proposes to revise § 314.50 by adding a new paragraph (i) that would contain the regulations implementing the statutory provision regarding the certification requirements and to add new § 314.52 to describe the notice requirements.

As with ANDA's, under proposed revised § 314.80, an applicant of an approved 505(b)(2) application would comply with the requirements for reporting adverse drug experiences only if the approval is effective under § 314.107

J. Applications for Changes in Approved Drug Products That Require the Review of Investigations

As described in part V section C., *supra*, an applicant may petition for permission to submit an ANDA for certain changes in the listed drug when the change does not require the review of investigations. An applicant may also wish to make a modification in an approved drug where the modification requires the submission of data that cannot be reviewed in an ANDA. For example, an applicant may wish to obtain approval of a new indication for a listed drug that is only approved for other indications. If the applicant has an approved ANDA for the approved indications, the applicant may of course submit a supplemental application that contains reports of clinical investigations needed to support approval of the new indication. (Because such a supplement would require the review of clinical data, FDA would process it as a submission under section 505(b) of the act.)

An applicant may also wish to seek approval of, for example, a new dosage form of a listed drug that requires the review of investigations but may have no interest in marketing the drug in its approved dosage form. The 1984 Amendments do not directly address the appropriate mechanism for obtaining approval of such a change, but permit several alternatives. The statute could be interpreted to require such an applicant to first obtain approval of an ANDA for the listed drug's approved dosage form, and then file a 505(b) supplement to the approved ANDA containing clinical data to obtain approval of the new dosage form. If the applicant did not first obtain an ANDA for the approved dosage form, the applicant could be required to submit a full new drug application under section 505(b) of the act for the new dosage form and duplicate the basic safety and effectiveness studies conducted on the listed drug. FDA has concluded that such an interpretation would be inconsistent with the legislative purposes of the 1984 Amendments because it would serve as a disincentive to innovation and could require needless duplication of research.

FDA believes that a more consistent, less burdensome interpretation of the 1984 Amendments is to allow a generic applicant to submit a 505(b) application for a change in an already approved drug that requires the submission and review of investigations, without first obtaining approval of an ANDA for a duplicate of the listed drug. Therefore, under proposed § 314.54, applications will be accepted for changes requiring the review of investigations, including changes in dosage form, strength, route of administration, and active ingredients (in a combination product), as well as new indications. Like similar supplements to approved ANDA's, these applications will rely on the approval of the listed drug together with the data needed to support the change. The applicant will thus be relying on the approval of the listed drug only to the extent that such reliance would be allowed under section 505(j) of the act: to establish the safety and effectiveness of the underlying drug. FDA notes, however, that it will not accept such an application for a drug that differs from the listed drug only in that its extent of absorption is significantly less than that of the listed drug. To allow such a drug to be approved under section 505(b)(2) would thwart Congress' clear intention to require that a duplicate of a listed drug be shown to be bioequivalent to that listed drug. (See section 505(j)(3)(F) of the act.)

FDA also believes that it would be inconsistent with the policies of the 1984 Amendments to allow these applications to rely on the approval of a listed drug unless they were subject to the listed

drug applicant's patent rights and exclusivity. Therefore, an application that relies in part on the approval of a listed drug, is, for this purpose, considered an application described in section 505(b)(2) and must make a certification as to any relevant patents that claim the listed drug. In addition, the date of submission and effective approval of these applications may, under section 505(c)(3), be delayed to give effect to any patent or period of exclusivity accorded the listed drug.

Because these submissions will be reviewed as applications under section 505(b) of the act, they will be subject to the statutory and regulatory requirements applicable to such applications, including the patent submission requirements of sections 505 (b) and (c) of the act, and may be eligible for 3 years of exclusivity under sections 505(c)(3)(D) (iii) and (iv) of the act. These applications should be directed to the address specified in § 314.440(a)(1). The agency proposes to revise § 314.440(a)(1) to so state.

K. Delay in the Effective Date of Approval of an ANDA and 505(b)(2) Application Because of the Existence of a Patent

The 1984 Amendments require an important change from previous practice for ANDA's and those 505(b)(2) applications previously handled as paper NDA's with respect to the effective date of their approval. The effective dates of approval of ANDA's and 505(b)(2) applications are dependent on the existence of any patents on the pioneer drug for which the generic applicant is seeking approval (sections 505(j)(4)(B) and 505(c)(3) of the act) and on any periods of exclusive marketing accorded the reference listed drug or other listed drug under the so-called "exclusivity" provisions of the act (sections 505(j)(4)(D) and 505(c)(3)(D) of the act). Thus, an ANDA or 505(b)(2) application may be approved with a delayed effective date, as specified by the agency in its approval letter. No new drug product may be introduced or delivered for introduction into interstate commerce under a full or abbreviated new drug application unless the approval of the application is effective (section 505(a) of the act). The agency proposes to add new § 314.107 to the regulations to codify the statutory requirements with respect to effective dates of approval of ANDA's and 505(b)(2) applications.

With respect to patent status, proposed § 314.107 provides that approval of an ANDA or 505(b)(2) application, if approval is otherwise warranted, would be made effective in accordance with the following conditions. First, if the applicant certified that there are no relevant patents, or the holder of the approved application for a drug product covered by a relevant patent did not submit to FDA any patent information, or that the relevant patents submitted to FDA have expired, approval of the ANDA or 505(b)(2) application would be made effective immediately.

Second, if the applicant certified that any relevant patents would expire on a certain future date, based on information submitted to FDA, approval of the ANDA or 505(b)(2) application would become effective on that date, unless that date had already passed, in which case the approval would be immediately effective.

Third, if the applicant certified that any relevant patent was invalid or would not be infringed, approval of the ANDA or 505(b)(2) application could be made effective 45 days from the date of the receipt of the notice of certification by the patent owner or the approved application holder who is an exclusive patent licensee, unless the patent owner or exclusive patent licensee filed an action for patent infringement before the 45 days have elapsed. As discussed in part V section D.1.j. above, FDA proposes to require that an applicant who has obtained a patent license to manufacture a generic copy of a patented drug certify under section 505(b)(2)(A)(iv) or 505(j)(2)(A)(vii)(IV) of the act that the relevant patent is invalid or will not be infringed. Although the statute does not expressly address the effect of patent licensing agreements on effective dates, FDA does not believe that Congress intended to interfere with such agreements between pioneer and generic drug manufacturers. See section 505(b)(1) of the act (defining applicable patents as those "to which a claim of patent infringement would reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug"). Accordingly, FDA proposes to make the approval of an ANDA or 505(b)(2) application effective immediately where the applicant submits (1) information establishing that the proposed drug is covered by a patent licensing agreement with the patent owner, and (2) a written statement from the patent owner consenting to an immediate effective date. FDA invites comment on this approach.

Even in the absence of a licensing agreement, the patent owner or exclusive patent licensee may waive its opportunity to file an action for patent infringement provided it submits a valid waiver to FDA before the 45 days elapses. Under proposed § 314.107(f)(3), if a patent owner or exclusive patent licensee does not intend to file action for patent infringement against the generic applicant within the 45-day time period and the applicant seeks an effective approval date before the 45-day period has elapsed, the patent owner or exclusive patent licensee must submit to FDA a waiver in the form prescribed in the proposed regulation.

1. *The 45-day clock.* Both the PMA and the Generic Pharmaceutical Industry Association (GPIA) offered FDA suggested regulatory language designed to ensure that the recipient of a notice of patent certification has the full 45 days in which to decide whether to bring a patent infringement suit. (PMA and GPIA comments filed under Docket No. 85N-0214.) FDA believes its proposed requirements under § 314.52 for an application submitted under section 505(b)(2) of the act and § 314.95 for an ANDA under section 505(j) of the act with respect to documentation of receipt of notice of certification and the proposed requirements in § 314.107 address the concerns of the PMA and GPIA. Under this proposal, the 45-day clock would begin on the day after the date of receipt by the patent owner or its representative or by the approved application holder if the holder is an exclusive patent licensee of the applicant's notice of certification. Thus, the applicant's return receipt or a letter acknowledging receipt from the patent owner or exclusive patent licensee would be deemed to be legal notice of receipt of the applicant's notification by the patent owner or its representative or exclusive patent licensee. Action would then have to be filed in federal court by the patent owner or exclusive patent licensee before the end of the 45th day.

In computing the 45 days, Saturdays, Sundays, and Federal holidays are included. When, however, the 45th day falls on Saturday, Sunday, or on a Federal holiday, the 45th day would be the next succeeding day that is not a Saturday, Sunday, or a Federal holiday. FDA intends to strictly apply the 45-day statutory time period. Therefore, unless FDA is notified in writing by the ANDA or 505(b)(2) applicant before the expiration of the 45-day time period or before the completion of the review period, whichever is later, of the commencement of legal action for patent infringement within the 45-day time period, approval of the ANDA or 505(b)(2) application may be made effective immediately upon expiration of the 45 days or upon completion of the review process, whichever is later. Even

if the commencement of legal action occurs before the ANDA is ready for approval but after the 45-day period has elapsed, the agency will approve the ANDA with an immediate effective date when the application review is complete and satisfactory. Notification by the generic applicant of the filing of a complaint alleging patent infringement shall include: (1) the ANDA or 505(b)(2) application number, (2) the ANDA or 505(b)(2) applicant's name, (3) established name of the drug, if any, strength, and dosage form, and (4) a certification that action to defend the patent, identified by number, has been filed in an appropriate court and the date of the filing. An ANDA applicant shall submit the notification to FDA's Division of Generic Drugs (HFD–230); a 505(b)(2) applicant shall submit the notification to the appropriate division in the Center for Drug Evaluation and Research reviewing the application.

If an action for patent infringement is filed before the expiration of the 45 days, FDA is precluded from making the approval of the ANDA or 505(b)(2) application effective for a period of 30 months while the matter is in litigation or until a date of a final decision determined by a court, with one exception. The exception is for a patented drug entitled to 5 years of marketing exclusivity under section 505(c)(3)(D)(ii) or (j)(4)(D)(ii) of the act, where the patent holder files an action for patent infringement during the 1-year period beginning 4 years after the date the patented drug was approved (and within 45 days of receiving the notice of patent certification). In this situation, FDA must extend the 30-month period by that amount of time required for 7½ years to elapse from the date of approval of the patented drug. Once the 30 months, or 7½ years where applicable, have expired, the applicant would have an effective approval of its drug product subject to the outcome of the pending litigation, unless the court itself orders otherwise.

If before the expiration of the 30-month or 7½-year period the court decides that any relevant patent is invalid or not infringed, approval of the ANDA or 505(b)(2) application would be made effective on the date that final judgment is entered by the court.

If before the expiration of the 30-month or 7½-year period the court decides that any relevant patent would be infringed, the approval would be made effective on the date the patent expires or on the date the court orders. If before the expiration of the 30-month or 7½-year period the court grants a preliminary injunction prohibiting an applicant from manufacture or marketing of its drug product until the court decides the issues of patent validity and infringement and if the court later decides that the patent is invalid or not infringed, approval would be made effective on the date the court enters final judgment on the merits.

For purposes of establishing the proper effective date for an ANDA or 505(b)(2) application approval in the above situations, FDA proposes that the applicant submit to the Division of Generic Drugs (HFD–230), within 10 working days of the entry of any relevant judgment, a copy of the court order. There is a potential ambiguity in the statutory language concerning what "court" decision triggers an effective date. The agency has interpreted that language as referring to the final decision of that court from which no appeal can be or has been taken by the affected party.

FDA will issue a revised approval letter stating the effective approval date. However, an applicant may begin marketing its approved drug product on the date that final judgment is entered by the court or on any other court ordered effective date whether or not the applicant has received a revised approval letter from FDA.

2. *The 180-day exclusivity period.* Finally, under the proposal and the statute, if any subsequent ANDA's for the same drug product as the first drug product to be involved in a patent infringement action also contain a certification of the invalidity or noninfringement of a patent, approval of those subsequent ANDA's would not become effective until 180-days after the first commercial marketing of the drug product under the first ANDA, or until 180 days after the court has determined that the patents in dispute are invalid or not infringed, whichever is earlier. (See section 505(j)(4)(B)(iv) of the act.) This provision does not apply to 505(b)(2) applications.

FDA has concluded that the 180-day delay of subsequent ANDA's is available only to a previous applicant who has been sued for patent infringement following its notification to the patent owner of the filing of a certification of invalidity and noninfringement. Although section 505(j)(4)(B)(iv) of the act can be interpreted in several ways, FDA believes that the structure of the provision reflects Congress' intention to provide to the first generic applicant who spends its resources to litigate the scope or validity of a patent a 180-day period free from generic competition.

The formula provided by section 505(j)(4)(B)(iv) of the act for calculating the date from which the 180-day period runs, and particularly the reference to "first commercial marketing, can be applied logically and consistently with the statutory scheme only if Congress intended the provision to apply only when the first ANDA applicant was actually sued for patent infringement. Every other exclusivity provision in the 1984 Amendments begins with date of approval of the application. Congress' decision to begin the 180-day period under section 505(j)(4)(B)(iv)(I) of the act from "the first commercial marketing of the drug, rather than from the effective date of the ANDA, serves a rational policy only if Congress contemplated a situation in which an approval of an ANDA is in effect but the applicant's decision not to market the drug deserves to be protected because a delay in marketing serves the public interest.

Such a situation occurs where, under the terms of section 505(j)(4)(B)(iii) of the act, an ANDA goes into effect 30 months after a lawsuit is filed, but the lawsuit is still pending. It serves the public interest to permit a prudent ANDA holder in that situation to stay off the market until the litigation is resolved, thereby minimizing potential damages.

As drafted, sections 505(j)(4)(B)(iv)(I) and (II) of the act carefully avoid providing an incentive for immediate marketing: the 180-day reward of exclusive marketing begins when the applicant wins the lawsuit or when the applicant actually begins marketing, "whichever is earlier. The applicant thus does not lose any of the 180-day period by electing to stay off the market until the lawsuit is over.

If, on the other hand, section 505(j)(4)(B)(iv) of the act is interpreted to apply even if the first applicant has not been sued, dating the 180-day period from "first commercial marketing" rather than from the effective date of the ANDA approval serves no purpose. Indeed, it might provide a counterproductive incentive to the first ANDA applicant to delay marketing so as to prolong the period during which other ANDA's may not be marketed. In contrast to the delay occasioned by a prudent plaintiff in a lawsuit, this delay serves no public interest. To remove this unproductive incentive for delay, the agency would therefore consider it necessary to read into section 505(j)(4)(B)(iv)(I) of the act various additional requirements and presumptions.

Section 505(j)(4)(B)(iv) can thus be applied straightforwardly only when an

applicant who seeks the 180-day period of exclusive marketing has been involved in a patent infringement lawsuit. To apply the section where there has been no lawsuit, requires either that the agency ignore the plain language of the section, essentially reading out the phrase "first commercial marketing, or that the agency assume, contrary to the goals of the 1984 Amendments, that Congress intended to create an incentive for delay in competition, without any countervailing benefit to society. Moreover, the policy embodied in the provision, of rewarding the applicant who devotes the considerable time and money necessary for patent litigation, is not served by providing 180 days of exclusive marketing to an applicant who avoids a lawsuit. Accordingly, proposed § 314.107(c) applies only when the first applicant has been sued.[1]

FDA has also concluded that the 180-day period of exclusivity delays approval of all generic copies of the same listed drug whose applications contain paragraph IV certifications. It has been suggested that where a formulation or composition patent is the subject of certification and lawsuit, the exclusivity granted under section 505(j)(4)(B)(iv) should delay the effective approval only of subsequent applications that raise claims of noninfringement identical or similar to those raised by the holder of the exclusivity. The legislative history of section 505(j)(4)(B)(iv) is silent as to the purpose of the provision and does not limit its applicability to subsequent applicants that receive a benefit from the first applicant's finding of noninfringement. The 180-day period can be interpreted as a reward not only for the benefit provided to subsequent ANDA applicants but for the benefit to the public of removing an obstacle to competition. Moreover, FDA lacks the expertise in patent law that would allow it to determine whether a subsequent applicant raised issues of noninfringement in common with the previous applicant. Therefore, the 180-day period is available to the applicant who resolves an issue of patent coverage, regardless of the judgment's applicability to subsequent ANDA applicants.

3. *Other provisions.* FDA proposes to implement other aspects of section 505(j)(4)(B)(iv) of the act as follows:

a. *Date of submission.* The date of submission of a prior application that contained a certification of invalidity or noninfringement will be considered the date on which the applicant submitted a substantially complete ANDA. In most cases, to be "substantially complete, an ANDA must contain data from any required bioavailability or bioequivalence studies. A required bioequivalence study is one that meets any FDA guidance document or is otherwise reasonable in design and purports to show that the drug product for which the applicant seeks exclusivity is bioequivalent to the listed drug. Neither a protocol nor a pilot study will satisfy these requirements. (An ANDA may be substantially complete without such studies only if such studies are not required to establish bioequivalence, i.e., where bioequivalence can be established through other information and the applicant has requested a waiver of the study requirements.) Although the provision could be read to permit the mere submission of the first certification of invalidity or noninfringement to delay the effective date of subsequent ANDA's, regardless of the completeness of the application, the legislative history of the 1984 Amendments makes clear that such an interpretation would be inconsistent with the purposes of the patent certification and notification scheme.

The purpose of section 505(j)(4)(B)(iv) of the act is to reward the first applicant to test the scope or validity of a patent by litigating an action for patent infringement. However, it is only the giving of notice to the patent owner under section 505(j)(2)(B)(ii) of the act, and not the filing of a certification of invalidity or noninfringement with FDA, that can initiate a lawsuit. The notice required by section 505(j)(2)(B)(ii) of the act must state that the applicant has submitted an ANDA "which contains data from bioavailability or bioequivalence studies. (Section 505(j)(2)(B)(ii) of the act.) The purpose of requiring a statement that the ANDA contains data from bioavailability or bioequivalence studies is to prevent applicants from testing an innovator's patent through the filing of "sham ANDA's or ANDA's that are substantially incomplete. H. Rept. 98 857 Part I, 98th Cong., 2d Sess. 24–5 (1984).

FDA believes that to fulfill the purposes of the patent provisions of the statute, the date of submission of a previous application under section 505(j)(4)(B)(iv) of the act must therefore be the date on which the previous applicant submitted a substantially complete ANDA, and thus was in a position to notify the patent owner. As described in part V section E., supra, an ANDA that contains a certification of invalidity or noninfringement will not be accepted for review unless it contains the results of any required bioequivalence studies.

b. *Delay when first application is not yet approved.* If the first ANDA applicant for a listed drug is sued for patent infringement and a subsequent ANDA for the drug is submitted before the first ANDA is approved, FDA will delay the effective date of approval of the subsequent ANDA only as long as the agency remains satisfied that the first applicant is actively pursuing approval of its ANDA.

c. *"First commercial marketing.* "First commercial marketing" is defined as the first date of introduction or delivery for introduction into interstate commerce outside the control of the manufacturer, except for investigational use under 21 CFR Part 312, but does not include transfer of a drug product for reasons other than sale within the control of the manufacturer or application holder.

d. *"Court decision."* Section 314.107(c)(1)(ii) specifies as one of the two dates from which the 180 days runs "the date of a decision of the court holding the patent invalid or not infringed. This date will be the date of a final decision of a court from which no appeal can or has been taken, or the date of a settlement order or consent decree signed by a Federal judge, which enters final judgment and includes a finding that the patent is invalid or not infringed. A final adjudication on the merits is not required to trigger the 180-day period.

e. *Amended certification after finding of infringement.* If a final judgment is entered in an action for patent infringement finding the patent to be infringed by a drug product that is the subject of an abbreviated new drug application, and the application contains a paragraph IV certification, the applicant should submit an amended certification, certifying under § 314.94(a)(12)(i)(A)(3) that the patent will expire on a specific date. The new certification should be submitted either as an amendment to a pending application or as a letter if the application is approved. Once the amendment or letter has been submitted, the application will no longer be considered to be one containing a paragraph IV certification.

f. *Amended certification after removal of a patent from the list.* If, after one or

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Note: Subsequent to the Commissioner's signing of this document, Federal district court reached contrary conclusion. See Inwood v. Young, No. 89–0845 (D.D.C. May 12, 1989). An appeal from that decision is under consideration.

more applicants have made paragraph IV certifications on a patent, that patent is removed from the list for any reason other than because that patent has been declared invalid in a lawsuit brought by that patent owner within 45 days of receiving notice under § 314.95 any applicant with a pending application or delayed effective date who has made such a certification should submit an amended patent certification, certifying under § 314.94(a)(12)(ii) if applicable, that no relevant patents claim the drug. If other relevant patents still claim the drug, the applicant should instead submit a request to withdraw the paragraph IV certification. Once the amendment or letter has been submitted, the application will no longer be considered to be an application containing a paragraph IV certification.

L. Exclusivity

1. *Exclusivity for certain approved drug products.* Sections 505(j)(4)(D) and 505(c)(3)(D) of the act partially protect certain listed drugs, or certain changes in listed drugs, from competition in the marketplace for specified periods by placing a moratorium on the submission of, or by delaying the effective date of approval of, ANDA's and 505(b)(2) applications for those listed drug products. (The exclusivity provisions of the act do not provide any protection from the marketing of a generic version of the same drug product if the generic version is the subject of a full new drug application submitted under section 505(b)(1) of the act.) These periods of exclusive marketing are independent of any marketing exclusivity accorded an orphan drug pursuant to section 527 of the act and of any protection a listed drug may have as a result of a patent. Proposed § 314.108 implements the exclusivity provisions of sections 505(j)(4)(D) and 505(c)(3)(D) of the act. The holder of a new drug application or supplemental new drug application submitted under section 505(b) of the act that was approved on or after January 1, 1982, may be entitled to a period of exclusive marketing (hereinafter referred to as "exclusivity") for the drug product subject to the approved application or supplemental application.

Briefly, the exclusivity provisions provide the following protection. Sections 505(c)(3)(D)(i) and 505(j)(4)(D)(i) grant a 10-year period of exclusivity to new chemical entities approved during a specified "window period": January 1, 1982, to September 24, 1984, the date of enactment of the 1984 Amendments. Sections 505(c)(3)(D)(ii) and 505(j)(4)(D)(ii) of the act grant a 5-year period of exclusivity to new chemical entities approved after September 24, 1984. Sections 505(c)(3)(D)(v) and 505(j)(4)(D)(v) of the act grant a 2-year period of exclusivity for non-new chemical entities, or for certain changes made to already approved products, approved during the "window period. (This 2-year period expired on September 24, 1986.) There is no requirement that an applicant have conducted clinical investigations to qualify a drug for exclusivity under the above three provisions. On the other hand, the remaining two exclusivity provisions, sections 505(c)(3)(D)(iii) and (iv) and 505(j)(4)(D)(iii) and (iv) of the act, which grant a 3-year period of exclusivity, specifically require that the applicant have "conducted or sponsored new clinical investigations essential to the approval" of the application, or the supplement.

With the exception of the 2-year exclusivity provision for non-new chemical entities or changes approved between January 1, 1982, and September 24, 1984 (sections 505(j)(4)(D)(v) and 505(c)(3)(D)(v) of the act), the exclusivity provisions are limited to new chemical entities, which by definition are innovative, and to those significant changes in already approved drug products, such as a new use, which require new clinical studies. Congress understood that the substantial economic rewards of exclusivity might well encourage drug companies to make minor and unimportant alterations in their marketed drug products or to conduct additional tests which they could claim provide important new information about a marketed drug product. To avoid rewarding such behavior, the 3-year provision includes the special criteria intended to restrict eligibility to significant innovations. See Cong. Rec. H9114, 9124 (daily edition September 6, 1984) (statement of Representative Waxman); Cong. Rec. S10505 (daily edition August 10, 1984) (statement of Senator Hatch).

The exclusivity provisions of section 505(j)(4)(D) of the act operate to prohibit the submission or delay the effective date of approval of (1) an ANDA submitted under section 505(j) of the act for a duplicate of a listed drug that is entitled to exclusivity and (2) an ANDA submitted under section 505(j) of the act pursuant to an approved petition under section 505(j)(2)(C) of the act for a drug product that is similar to a listed drug that is entitled to exclusivity. The exclusivity provisions of section 505(c)(3)(D) of the act affect applications described under section 505(b)(2) of the act and are essentially the same as those for abbreviated new drug applications. The legislative history of the 1984 Amendments makes clear that Congress intended the exclusivity provisions of section 505(c)(3)(D) of the act to delay submission or approval of applications described by section 505(b)(2) of the act to the same extent that section 505(j)(4)(D) of the act delays submission or approval of ANDA's. Section 505(c)(3)(D) of the act, however, unlike section 505(j)(4)(D) of the act, could be interpreted to apply only to those 505(b)(2) applications that are required to submit a patent certification. (See section 505(c)(3) of the act.) Under this interpretation, applications described by section 505(b)(2) of the act that were not required to submit a patent certification because, for example, the pioneer drug was unpatentable, would be exempt from the exclusivity provisions of section 505(c)(3)(D) of the act.

The agency does not believe that this interpretation is reasonable and intends to apply section 505(c)(3)(D) of the act to all 505(b)(2) applications. Although section 505(c)(3) of the act states that the delayed effective dates specified in section 505(c)(3)(A) through (D) apply to "an application filed under subsection (b) which contains a certification required by paragraph (2) of such subsection, patent certification is relevant only to section 505(c)(3)(A) through (C) of the act. These paragraphs delay an application's effective date on the basis of the patent status of the pioneer drug. Section 505(c)(3)(D) of the act, however, delays an effective date on the basis of exclusivity, which is entirely independent of the patent status of the pioneer drug. Indeed, in the floor debates preceding enactment of the 1984 Amendments, Congressman Waxman specifically stated that one of the purposes served by the exclusivity provisions was to supply needed incentives to develop new drugs where little or no patent life remains. Cong. Rec. H9113 (daily edition, September 6, 1984). It would thus be illogical and inconsistent with Congressional intent to apply the exclusivity provisions only to those 505(b)(2) applications required to make a patent certification.

Exclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product. Thus, if the innovation relates to a new active moiety or ingredient, then exclusivity protects the pioneer drug product from other competition from products containing that moiety or ingredient. If the innovation is a new dosage form or route of administration, then exclusivity protects only that

aspect of the drug product, but not the active ingredients. If the innovation is a new use, then exclusivity protects only that labeling claim and not the active ingredients, dosage form, or route of administration.

The language of sections 505(c)(3)(D) and 505(j)(4)(D) of the act is ambiguous as to which ANDA's or 505(b)(2) applications are affected by an innovator's exclusivity. The statutory language allows at least two interpretations. The narrower interpretation of the protection offered by exclusivity is that exclusivity covers only specific drug products and therefore protects from generic competition only the first approved version of a drug, or change in a drug. Under this interpretation, an innovator's exclusivity could lose its value as soon as FDA approved a second full new drug application for a version of the drug, because an ANDA could be approved by reference to the second approved version of the drug, which would not be covered by exclusivity.

The broader interpretation of the coverage of exclusivity is that it covers the active moieties in new chemical entities or changes in non-new chemical entities rather than covering only specific drug products. Thus exclusivity would protect the new active moiety of a new chemical entity or the innovative change in a non-new chemical entity from generic competition even after FDA had approved subsequent full new drug applications for subsequent versions of the drug. Under this theory, an ANDA or 505(b)(2) application for a drug with the same active moiety as the innovator's new chemical entity or as the innovator's change in a non-new chemical entity could not be approved until the innovator's exclusivity expired, even if the ANDA or 505(b)(2) application relied on another approved version of the innovator's drug.

The language of the five exclusivity provisions (similarly worded in both sections 505(c)(3)(D) and 505(j)(4)(D) of the act) is inconsistent on this issue, tending to support the narrower interpretation of the coverage of exclusivity for new chemical entities (sections 505(c)(3)(D) (i) and (ii) and 505(j)(4)(D) (i) and (ii) of the act and for drugs approved between January 1, 1982, and September 24, 1984 (sections 505(c)(3)(D)(v) and 505(j)(4)(D)(v) of the act), and the broader interpretation for innovative changes in already approved drugs (sections 505(c)(3)(D) (iii) and (iv) and 505(j)(4)(D) (iii) and (iv) of the act). Sections 505(c)(3)(D) (i), (ii), and (v) and 505(j)(4)(D) (i), (ii), and (v) of the act confer exclusivity by prohibiting submission or delaying approval of ANDA's or 505(b)(2) applications that "refer to the drug for which the [first approved] subsection (b) application was submitted. Depending upon the meaning of the phrase "refer to" and the word "drug, these provisions could be interpreted to allow ANDA's and 505(b)(2) applicants, once FDA approved subsequent new drug applications for different versions of the same drug, to circumvent the innovator's exclusivity by "referring to" the subsequent versions of the innovator's drug.

On the other hand, the two provisions that confer exclusivity on changes in already approved drugs delay the effective date of approval of all ANDA's or 505(b)(2) applications that have the same "conditions of approval" as the innovator's drug, without regard to whether the ANDA "refers to" the innovator's drug product or to another version of the same product for which a subsequent new drug application was approved.

FDA does not believe that Congress intended the exclusivity provisions to operate inconsistently, or that Congress intended the protection offered by the exclusivity for changes in approved drugs to be broader than the protection offered by exclusivity for new chemical entities. FDA therefore proposes to adopt a uniform interpretation of the scope of exclusivity. In addition, FDA has concluded that adopting the narrower interpretation of the scope of exclusivity for all types of exclusivity would seriously undermine its value, reducing the incentives for research and innovation in the pharmaceutical industry.

For example, if FDA adopted the narrower interpretation that exclusivity covers only a specific drug product and does not prevent ANDA s from copying subsequent versions of the innovative product, a manufacturer of a new chemical entity (entitled to 5 years of exclusivity), could not make improvements in the drug, e.g., by making a new dosage form of the drug, without destroying the value of its exclusivity. Approval of a new dosage form, and certain other changes in approved drugs, require the submission of a new drug application; once approved, the new dosage form would become a new drug product that an ANDA application could copy, without being subject to the exclusivity covering the original drug product.

For the same reasons, an innovator whose drug was entitled to exclusivity could not license another company to make a copy of the pioneer drug without losing the value of its exclusivity. Under the narrow theory of exclusivity, once the licensed company's product was approved, ANDA applicants could copy the licensed product, without regard to the innovator's exclusivity.

The agency does not believe that Congress intended the exclusivity provisions to discourage innovators from making improvements in their drug products nor from authorizing the marketing of competitive products. Accordingly, FDA has concluded that the broader interpretation of the scope of exclusivity should be applied to all types of exclusivity conferred by sections 505(c)(3)(D) and 505(j)(4)(D) of the act.

Therefore, when exclusivity attaches to an active moiety or to an innovative change in an already approved drug, the submission or effective date of approval of ANDA's and 505(b)(2) applications for a drug with that active moiety or innovative change will be delayed until the innovator's exclusivity has expired, whether or not FDA has approved subsequent versions of the drugs entitled to exclusivity, and regardless of the specific listed drug product to which the ANDA or 505(b)(2) application refers.

Proposed new § 314.108 implements the exclusivity provisions with respect to both ANDA's and 505(b)(2) applications.

a. *Definitions.* To understand how the agency intends to administer the exclusivity provisions of the act, it is necessary to define a number of terms that are used in those provisions. Some of those definitions have already been discussed; others are as follows:

1. *New chemical entity.* "New chemical entity" means a drug that contains no active moiety that has been approved by the Food and Drug Administration in any other application submitted under section 505(b) of the act. Thus, FDA interprets the statutory requirement that a drug (new chemical entity) contain "no [previously approved] active ingredient (including any ester or salt of the active ingredient)" to mean that the drug must not contain any previously approved active moiety. FDA bases this interpretation on the statutory language and on the definition of a "new molecular entity" or "Type 1" drug in FDA's IND/NDA classification scheme (which is used to classify new drugs by chemical type and therapeutic significance), which was in effect at the time the 1984 Amendments were under consideration in Congress. FDA's longstanding interpretation of the term "new molecular entity" is that it is a compound containing an entirely new

active moiety. FDA's interpretation of the scope of the 5-year exclusivity provision is also consistent with the legislative history, which reveals that Congress was aware of FDA s classification scheme and did not intend to confer significant periods of exclusivity on minor variations of previously approved chemical compounds. (See, e.g., Cong. Rec. H9124 (September 6, 1984) (statement of Representative Waxman); H. Rept. 857 Part I, 98th Cong., 2d Sess. 38 (1984).)

ii. *Active moiety.* The "active moiety" in a drug is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance. A drug product will thus not be considered a "new chemical entity" entitled to 5 years of exclusivity if it contains a previously approved active moiety, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative has not been previously approved. A compound (other than an ester) that requires metabolic conversion to produce an already approved active moiety is considered a "new molecular entity, however, and will be considered a new chemical entity entitled to 5 years of exclusivity. FDA will consider whether a drug contains a previously approved active moiety on a case-by-case basis. FDA notes that a single enantiomer of a previously approved racemate contains a previously approved active moiety and is therefore not considered a new chemical entity.

iii. *Date of approval.* An issue has arisen as to how the date of approval of a new drug application is determined. This issue is particularly important when an applicant is claiming that its new drug application was approved between January 1, 1982, and September 24, 1984, referred to in sections 505(c)(3)(D) (i) and (v) and 505(j)(4)(D) (i) and (v) of the act of the exclusivity provisions. The "date of approval" of the application as used in these provisions means the date on the approval letter sent by FDA to the applicant. A requirement in the approval letter for submission (but not for approval) of final printed labeling or other material that might delay the actual initiation of marketing of the product is not relevant to a determination of the date of approval, so long as the product could be legally marketed. Two cases have addressed FDA's interpretation of "date of approval. *Mead Johnson Pharmaceutical Group* v. *Bowen,* 838 F.2d 1332 (D.C. Cir. 1988), and *Norwich Eaton Pharmaceuticals, Inc.* v. *Bowen,* 808 F.2d 486 (6th Cir.), *cert. denied,* 108 S. Ct. 68 (1987). In these cases, two separate drug manufacturers challenged FDA's determinations that their products were not entitled to 10 years of exclusivity under sections 505(c)(3)(D)(i) and 505(j)(4)(D)(i) of the act, which grant such exclusivity to certain products approved between January 1, 1982, and September 24, 1984. FDA's determinations were based on its position that the two drugs were approved on the date the approval letters were issued, in both cases prior to January 1, 1982. The plaintiffs argued that the date of approval did not occur until the firms submitted final printed labeling. In both cases, the courts upheld FDA's position that the date an approval letter issues is the date of approval of a new drug application.

b. *Periods of exclusivity.* Drug products that are the subject of the following types of applications are eligible for specified periods of exclusivity.

i. Sections 505(c)(3)(D)(i) and 505(j)(4)(D)(i) of the act provide exclusivity for a drug product containing a new chemical entity that is the subject of a new drug application submitted under section 505(b) of the act and approved during the period beginning January 1, 1982, and ending on September 24, 1984. The approval of an ANDA or 505(b)(2) application for a drug product that contains the same active moiety as the listed drug may not become effective for 10 years after the date of approval of the listed drug entitled to exclusivity. Thus, a drug product covered by an ANDA or a 505(b)(2) application would be subject to a listed drug's 10-year exclusivity if it contains the active moiety in the listed drug.

A drug product is entitled to 10 years of exclusivity only if it does not contain an active moiety that has been part of a drug product previously approved under section 505(b) of the act either as a single ingredient or as one ingredient of a combination drug product. An application is one "approved under section 505(b)" if it was submitted under section 505(b) of the act and approved after the passage of the 1962 Amendments to the act or was "deemed approved" under section 107(c)(2) of the 1962 Amendments. Because the exclusivity conferred by this provision covers the active moiety of a drug, the exclusivity also protects a different ester or salt or other noncovalent derivative, or a different dosage form, strength, route of administration, or condition of use approved in a subsequent application or supplemental application for a drug product containing the same active moiety. Any modification in dosage form, strength, route of administration, or indication of a new chemical entity entitled to 10 years of exclusivity will be protected for the period of exclusivity remaining on the original application. Different salts, esters, or other changes that do not result in a change in active moiety are also protected. Significant changes to the drug product that occur after or toward the end of the initial 10 years of exclusivity and that independently qualify for exclusivity, e.g., a new use requiring new clinical investigations for approval (see discussion under provision d. below) may result in an additional period of exclusivity, but only for the change.

ii. Sections 505(c)(3)(D)(ii) and 505(j)(4)(D)(ii) of the act provide exclusivity for a drug product containing a new chemical entity that is the subject of a new drug application submitted under section 505(b) of the act and approved after September 24, 1984. No ANDA or 505(b)(2) application for a drug product that contains an active moiety in the listed drug may be submitted to FDA before the expiration of 5 years after the date of approval of the application for the listed drug entitled to exclusivity, except that an application challenging a patent that claims the listed drug may be submitted 4 years after approval of the listed drug. In the latter case, because this exclusivity provision blocks only submission of the ANDA or 505(b)(2) application, approval of the ANDA or 505(b)(2) application properly submitted after 4 years is not delayed by this provision, unless the patent owner initiates a lawsuit for patent infringement. Where litigation is initiated, the ANDA or 505(b)(2) application may not be made effective by FDA for a total of 7½ years after the approval of the reference listed drug, unless the court holds the patent invalid or not infringed at an earlier date. (See discussion under part V section K.)

As with sections 505(b)(3)(D)(i) and 505(j)(4)(D)(i) of the act, the agency interprets the exclusivity provided by this provision to cover any subsequent approval of an application or supplemental application for a different ester, salt, or other noncovalent derivative, or a different dosage form, strength, route of administration, or new

use of a drug product with the same active moiety. Any modification to the product will be protected for the period of exclusivity remaining on the original application, unless the change occurs after or toward the end of the initial 5 years of exclusivity and independently qualifies for exclusivity under another exclusivity provision. (See discussion under provision b.i. above.)

iii. Sections 505(c)(3)(D)(iii) and 505(j)(4)(D)(iii) of the act provide exclusivity for a drug product that does not contain a new chemical entity, is the subject of a new drug application submitted under section 505(b) of the act and approved after September 24, 1984, and which contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant. For example, a drug product containing a previously approved active ingredient may be approved for a new indication, dosage form, strength, or route of administration for which clinical studies are essential to approval. Exclusivity would be provided only if the clinical studies were "new, "essential to approval, and "conducted or sponsored by the applicant. If these requirements are met, approval of an ANDA or of a 505(b)(2) application for a duplicate drug product or an ANDA submitted pursuant to an approved petition under section 505(j)(2)(C) for a similar drug product that relies on the information supporting the new conditions of approval of the first-approved application, may not be made effective before the expiration of 3 years from the date of approval of the original new drug application.

iv. Sections 505(c)(3)(D)(iv) and 505(j)(4)(D)(iv) of the act provide exclusivity for a drug product that is the subject of a supplement to an approved application under section 505(b) approved after September 24, 1984, that contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the applicant. Approval of an ANDA submitted under section 505(j) of the act for a duplicate of, or submitted under section 505(j) of the act pursuant to an approved petition under section 505(j)(2)(C) of the act for a similar drug product that relies on the information supporting the new conditions of approval of a listed drug that is entitled to exclusivity or a 505(b)(2) application for a change approved in the supplemental application may not become effective for 3 years from the date of approval of the supplemental application. Under this provision, only the change approved in the supplemental application would be granted exclusivity and that exclusivity would be provided only if "new clinical investigations" were "essential to approval" of the change and the investigations were "conducted or sponsored by the applicant. The three requirements for exclusivity under this provision are identical to those of the third provision described above.

FDA expects that only those changes in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration or conditions of use would be granted exclusivity. These are the types of changes in a drug product that require prior approval by FDA before the change may be made (21 CFR 314.70).

To qualify for exclusivity under section 505(j)(4)(D) (iii) and (iv) of the act or section 505(c)(3)(D) (iii) and (iv) of the act, an application or supplemental application proposing a change to an already approved drug product must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant. All three of these criteria must be satisfied in order to qualify a drug product or change in a drug product for the exclusivity provided by these sections of the act.

Congress intended the term "clinical" to mean human studies, and intentionally excluded all animal studies, regardless of the purpose for which they are conducted. In *Zenith Laboratories, Inc.* v. *Heckler,* No. 85-3646 (D.N.J. May 19, 1986), Zenith Laboratories challenged the agency's interpretation of the term "clinical, arguing that clinical testing also includes animal testing. The court granted the government's motion for summary judgment, holding that FDA's interpretation was reasonable.

Further, Congress specifically excluded "bioavailability studies, which also may be clinical studies, to limit eligibility for exclusivity to changes in a drug product that are significant enough to require human safety or effectiveness studies for approval. The proposed regulations would, therefore, for purposes of exclusivity, define clinical investigation" to mean any experiment, other than a bioavailability study, in which a drug is administered or dispensed to, or used on, human subjects. The agency believes that most studies qualifying for exclusivity will be efficacy studies. There may, however, be occasional clinical investigations qualifying for exclusivity that establish that a product is safer than originally thought and that permit broader use of the drug. Studies that establish new risks will not be eligible for exclusivity because protection of the public health demands that all products' labeling contain all relevant warnings.

The legislative history makes clear that Congress intended to reward with 3 years of exclusivity only those investigations that require a considerable investment of time and money, see Cong. Rec. S10505 (daily edition August 10, 1984) (statement of Senator Hatch), and that are necessary for approval of important innovations requiring substantial study, such as significant new therapeutic uses, see Cong. Rec. H 9114, 9124 (daily edition September 6, 1984) (statements of Representative Waxman). The 3-year exclusivity provision, therefore, could be interpreted to confer exclusivity only for innovations requiring adequate and well-controlled trials in human subjects that meet the substantial evidence requirement for approval. Further, because the statutory language of this provision uses the term "clinical investigations" (plural) the provision could be interpreted to mean that more than one well-controlled trial is needed to support approval of the applicant's proposed change. The agency's interpretation of this exclusivity provision, however, is ordinarily to require only one clinical study and that it be of the type necessary to support approval of the proposed change.

The clinical investigations must be "new. Under this proposal, the agency would consider a clinical investigation "new" if the data from such a study (1) have not been relied on by the Food and Drug Administration to demonstrate substantial evidence of effectiveness of a previously approved drug for any indication or of safety for a new patient population and (2) do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patent population of a previously approved drug product. In this context, "new is intended to convey lack of prior use of this particular study or another similar study in successfully supporting the approval of the effectiveness of a drug product rather than any temporal requirement. The agency does not believe Congress intended to preclude use of data from a previously conducted study if such data provide important new information in support of the applicant's proposed change to its drug product. The agency would still consider to be "new data from a clinical investigation previously

submitted in a new drug application for use only in a comprehensive evaluation of the safety of a drug product but not to support the effectiveness of the drug product or safety in a specific new patient population.

Second, the studies referred to must also have been "conducted or sponsored by the applicant. PMA and GPIA submitted their views on this issue to the agency prior to publication of this proposal. (See Docket No. 85N-0214.) The PMA interpretation of "sponsored" would have that term apply whenever the applicant had provided financial, technical, or in kind support to the scientific studies, whether or not that support was the major funding of the investigations and whether or not it was received in advance of the performance of the investigations. GPIA disagreed, pointing out that the exclusivity provisions were intended to reward those who make a substantial investment and take the risk associated with clinical testing of a new drug or a new indication for a drug.

The Food and Drug Administration agrees that Congress intended these exclusivity provisions to reward only those who have made a substantial investment in new clinical studies. The underlying basis of exclusivity should, under the agency's policy, be transferable upon transfer of ownership of a company or rights to a drug. By making the product of the research more valuable, the agency believes this policy will foster and reward innovation and research to the full extent intended by Congress. However, the agency concludes that Congress did not intend that applicants qualify for exclusivity by simply collecting and submitting to FDA information from the literature, or buying the results of tests already done and submitting them to FDA. (See letter to Dr. Frank Young from Congressman Henry Waxman, August 5, 1985, on file in Docket No. 85N-0214.)

Therefore, in this proposal, the agency would consider an investigation "conducted or sponsored" by the applicant if, before or during the conduct of the investigation (1) the applicant was the sponsor of the IND under which the investigation was conducted, i.e., named as the sponsor of the IND in Form FDA-1571 filed with the agency, or (2) the applicant (or the applicant's predecessor in interest) provided substantial financial support for the study (see proposed § 314.108). For this purpose, the applicant's predecessor in interest may be a company the applicant purchased or merged with or a company that sold all rights to the drug to the applicant. Generally, if the applicant was the sponsor named in the Form FDA-1571 for a new clinical investigation that is essential to the approval, the applicant will be presumed to have conducted or sponsored that investigation. If the applicant was not the sponsor of the IND, e.g., because the study was conducted outside the United States, the applicant would be required to demonstrate sponsorship by showing that it provided substantial support for the study before it was completed. Ordinarily, to claim "substantial support, the applicant must have provided 50 percent or more of the cost of the study. In rare cases, the applicant may have provided less than 50 percent and still show "substantial support," if, for example, the study was extraordinarily expensive and the applicant's contribution to the total cost was significant. Merely supplying the drugs or providing other in kind support would not normally constitute "conducting or sponsoring" a study.

The applicant must show that its support for the study was provided before the study was conducted or while it was ongoing. The only exception to this rule is when, after completion of the study, the applicant purchased or merged with the company that sponsored or provided substantial support for the study or purchased all rights to the drug that is the subject of the application. Purchasing the study itself after the study has been completed does not constitute conducting or sponsoring a study. Under proposed § 314.50(j), an applicant would be required to include in its application (1) a statement that the applicant was the sponsor of the investigation named in Form FDA-1571 filed with the agency under the IND for the investigation, or (2) a certification with supporting information that the applicant or its predecessor in interest provided substantial support for the investigation. The agency acknowledges that it does not possess expertise and records essential to determining what elements should properly be considered in determining the cost of a study and what constitutes 50 percent funding of that study. The agency does not ordinarily intend to substitute its judgment for that of the applicant with respect to the 50 percent threshold. The agency will only look to see if the investigations were conducted under an IND in which the applicant was the sponsor or that the application contains the certification with supporting information. The agency specifically seeks comment on how to equitably interpret the term "sponsored by.

Third, the clinical studies must be "essential to the approval of the application. That is, without these new clinical studies, FDA would not have sufficient information to conclude that the drug product or change to a marketed drug product for which the applicant is seeking approval is safe and effective. Thus, to qualify for exclusivity, there must not be published reports of studies other than those conducted or sponsored by the applicant, or other information available to the agency sufficient for FDA to conclude that a proposed drug product or change to an already approved drug product is safe and effective. In addition, there must not be an already approved drug product for which the applicant could submit an ANDA or 505(b)(2) application. The agency disagrees with the suggestion by PMA that any "new information that will support the approvability of an application or supplement" is sufficient to satisfy this requirement. Rather, the studies must be truly "essential, rather than simply supportive, to qualify the application for exclusivity. A study will not be considered essential to approval merely because it was necessary for the applicant to conduct the study to avoid the exclusivity of the pioneer and obtain an immediate effective date of approval.

The PMA suggested regulatory language that it believed would help applicants to determine, in advance, the types of clinical investigations that would be considered "essential to the approval" of an application or supplemental application under section 505(b) of the act. The PMA urged FDA, upon request from a person planning to conduct or sponsor clinical tests on a proposed new drug, or upon submission of an IND, to examine a proposed testing protocol or general clinical outline to determine whether such clinical tests would be essential to approval of the new drug. PMA would have an investigation deemed essential unless FDA notified the applicant otherwise within 30 days following receipt of this information. GPIA opposed this PMA proposal.

What studies will be essential to the approval of an application cannot be determined, in each case, by a review of protocols without knowing what drugs have been approved and what is in the published literature at the time the application is approved. If published reports of investigations, other than those conducted or sponsored by the applicant, are sufficient to approve a drug product in a literature-supported application, no additional studies would be essential to the approval of that drug

product as of the date of approval. The agency encourages meetings between FDA and sponsors of clinical investigations to facilitate drug development and the approval process. However, the agency does not agree that it is possible to determine before approval which, if any, studies will be essential based on such discussions.

Under proposed § 314.50(j), an applicant would be required to include in its application a list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which the applicant is seeking approval. The list would be accompanied by a certification that the applicant has thoroughly searched the scientific literature and, to the best of the applicant's knowledge, the list is complete and accurate and, in the applicant's opinion, the listed studies or publicly available reports do not provide a sufficient basis for the approval of its application or supplement without reference to the new clinical investigation(s) in the application. The agency proposes that the applicant explain why the studies and reports are insufficient.

v. Sections 505(c)(3)(D)(v) and 505(j)(4)(D)(v) of the act provide exclusivity for a drug product that does not contain a new chemical entity and is the subject of a new drug application or supplemental application submitted under section 505(b) of the act and approved between January 1, 1982, and September 24, 1984. The approval of an ANDA or 505(b)(2) application that refers to the previously approved drug product or which refers to a change approved in a supplemental application may not be made effective before September 24, 1986. Because this date has passed, the proposed rule contains no reference to this provision.

Applications described in sections 505(b)(2) and 505(c)(3)(D) of the act present one issue not encountered with ANDA's. Because applications submitted under section 505(b) of the act may be entitled to exclusivity, there is an issue as to the treatment of concurrently pending 505(b)(2) applications for the same conditions of approval where the first approved 505(b)(2) application for a drug is entitled to exclusivity, and the approval of subsequent 505(b)(2) applications for that drug may be delayed. FDA proposes to interpret the exclusivity provisions with respect to competing 505(b)(2) applications in the following manner. Section 505(c)(3)(D)(ii), states that "* no application which refers to the drug for which the subsection (b) application [entitled to exclusivity] was submitted may be *submitted* (Emphasis added.) The agency intends to interpret this phrase to mean that any 505(b)(2) application submitted to FDA before the approval of another new drug application that qualifies for exclusivity under section 505(c)(3)(D)(ii) is not affected by this exclusivity provision. The agency believes, however, that an exception to this rule must be made where the first applicant to obtain approval and 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. FDA is proposing to amend § 314.60 to ensure that the competing applicant cannot, without a right of reference, rely on the first applicant's data and at the same time avoid the first applicant's exclusivity.

Under proposed § 314.60(b), an amendment submitted by the competing applicant to include reports of investigations conducted or sponsored by the exclusivity holder, to which the competing applicant had not obtained a right of reference, and which would be essential to the approval of the competing application, would cause the application to be deemed withdrawn and resubmitted. Because an application for a drug entitled to 5 years of exclusivity cannot be submitted until the exclusivity expires, the resubmission would not be accepted until the exclusivity had expired (or until the expiration of 4 years from the date the first application was approved, where the competing applicant sought to challenge a patent on the first applicant's drug).

The exclusivity provisions of sections 505(c)(3)(D) (iii) and (iv) of the act delay the effective date of approval of any 505(b)(2) application that is for the conditions of use of a previously approved application that contained new clinical investigations essential for approval. Consequently, if two 505(b)(2) applications are under review at the same time and one is approved before the other, the effective date of approval of the second application to be approved will be delayed, regardless of the date of submission, if the first contained new clinical investigations essential for approval and thereby qualified for exclusivity.

The issue of competing applications under section 505(c)(3)(D)(i) of the act is moot. No 505(b)(2) applications were submitted for any of the drug products qualifying for exclusivity under this provision before the approval of the qualifying applications.

2. *Exclusion of DESI upgrades from exclusivity.* Under FDA's DESI review, if a manufacturer had an effective new drug application for a drug product before 1962, FDA reaffirmed 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. This is known as a DESI upgrade.

The agency believes as a matter of policy and statutory interpretation that a grant of exclusivity is inappropriate for any DESI upgrade. Except for the 2-year exclusivity provision (sections 505(j)(4)(D)(v) and 505(c)(3)(D)(v) of the act), Congress carefully limited the exclusivity provisions of the statute to new chemical entities, which by definition were innovative, and to those changes in already marketed drug products, such as a new use, which are important innovations. A DESI upgrade does not constitute a change in a marketed drug or a major innovation; rather it permits the continued marketing of an already existing product for an already existing indication. Thus, FDA does not believe that DESI upgrades qualify for exclusivity. Changes in DESI drugs that were not shown to be effective in the DESI review may, however, be entitled to exclusivity.

3. *Challenges to exclusivity determinations.* Drug products that qualify for exclusivity under one of the statutory provisions discussed above are identified in FDA's list and its monthly supplements, which state the expiration date of the period of exclusivity for any listed drug that FDA believes qualifies for exclusivity. The authority to make final exclusivity determinations has been delegated to the Center for Drug Evaluation and Research's Office of Drug Standards. (See 52 FR 10881; April 6, 1987.)

Interested persons may disagree with the agency's findings with respect to a period of exclusivity accorded or not accorded a drug product. An interested person should first informally contact the agency to determine that the conclusion represented in the list is real and not an error. Having established that the entry or lack of entry in the list represents an agency finding, the interested person who disagrees with the finding should petition the agency pursuant to 21 CFR 10.25 to include, exclude, or revise exclusivity information in the list if the petitioner believes the information in the list is

incorrect. The agency will generally publish in the **Federal Register** a notice of availability of any such petition it receives. Such publication is constructive notice to all interested persons who may be affected by the petition. Persons who may be affected include holders of approved new drug applications, approved ANDA's and approved 505(b)(2) applications, applicants with pending applications or potential applicants. (See also 50 FR 39177· September 27 1985.)

To resolve exclusivity issues as early as possible in the drug approval process, FDA proposes that, if an applicant believes its drug product or change to an already marketed drug product is entitled to exclusivity under the act, the applicant include this information in its new drug application. Under proposed § 314.50(j) for a new drug product and proposed § 314.70(e) for a change to an already marketed drug product, an applicant would be required to include: (1) a statement that the applicant is claiming exclusivity for its drug product or change, if approved; (2) a reference to the provision under proposed § 314.108 that supports the claim; (3) if the applicant is claiming exclusivity under § 314.108(b)(2), information to show that no drug product has previously been approved under section 505(b) containing any active moiety in the drug product for which the applicant is seeking approval and (4) if an applicant is claiming exclusivity under proposed § 314.108(b) (4) or (5), information to show that the application contains "new clinical investigations, "essential to approval, of the application or supplement and "conducted or sponsored by" the applicant. (See discussion at part V section L.1., *supra.*)

M. Refusal to Approve ANDA's

The statutory grounds for refusing to approve an ANDA in part parallel the ANDA submission requirements. Thus, under proposed § 314.127 the agency would deny approval of an ANDA if (1) the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug product are inadequate to assure and preserve its identity, strength, quality, and purity; (2) information included in the ANDA is insufficient to show that each of the proposed conditions of use have been previously approved for the reference listed drug; (3) if the proposed drug product has one active ingredient, information in the ANDA is insufficient to show that the active ingredient is the same as that of the reference listed drug, or, if the proposed drug product is a combination product, (i) information in the ANDA is insufficient to show that the active ingredients are the same as those of the reference listed drug, or (ii) if one of the active ingredients differs, information in the ANDA is insufficient to show that the other active ingredients are the same as those of the reference listed drug, or that the differing 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 (iii) no petition to file an ANDA for the drug product with the different ingredient was approved under section 505(j)(2)(C) of the act; (4) information in the ANDA is insufficient to show that the route of administration, dosage form, or strength of the drug product are the same as those of the reference listed drug, or, if they are not the same, no petition to vary the changed elements was approved under section 505(j)(2)(C) of the act; (5) if the ANDA was filed pursuant to the approval of a petition to file an ANDA for a drug product with a different active ingredient, route of administration, dosage form, or strength, the ANDA did not contain the information required by FDA respecting the different active ingredient, route of administration, dosage form, or strength; (6) information in the ANDA is insufficient to show that the drug product is bioequivalent to the reference listed drug, or, if the ANDA was filed pursuant to an approved petition, the information 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 the same conditions of use; (7) information in the ANDA is insufficient to show that the labeling proposed for the drug product is the same as that for the reference listed drug except for changes required because of differences approved under a petition or because the drug product and reference listed drug are produced or distributed by different manufacturers.

1. *Inactive ingredients.* The statute also provides for denial of approval if information in the ANDA or any other information available to FDA shows that the inactive ingredients of the drug product are unsafe for use under the proposed conditions for use or that the composition of the drug product is unsafe under the proposed conditions of use because of the type or quantity of inactive ingredients in the drug product or the manner in which the inactive ingredients are included.

It is well-established that changing the inactive ingredients in a drug can adversely affect the drug's safety or effectiveness. Interpreting the act to require approval of generic drugs with potentially unsafe inactive ingredients would thwart one of the major purposes of the basic act, which was to prevent a repetition of the Sulfanilamide tragedy, in which the inactive ingredient of an untested drug was responsible for many deaths. The desire to avoid another such incident led to passage of the 1938 amendments to the act and the requirement that new drugs be shown to be safe. FDA is therefore proposing to consider inactive ingredients or composition "unsafe" if there is a reasonable basis to conclude that its inactive ingredients or composition raise serious questions about the drug's safety.

FDA's interpretation is consistent with the statutory scheme and with the purpose of the 1984 Amendments, which was to assure a supply of low cost generic drugs that are as safe and effective as their brand name counterparts.

Any other interpretation of section 505(j)(3)(H) of the act would produce absurd results when read in conjunction with the withdrawal provisions of section 505(e), which permit FDA to withdraw approval of an ANDA with less evidence of the hazard posed by an inactive ingredient than would be required to disapprove it. Section 505(e)(2) of the act permits FDA to withdraw approval of an application if there is evidence that shows that the drug "is not shown to be safe. FDA can invoke this provision if there is a reasonable basis from which to infer serious questions as to the safety of the drug, even if the agency lacks proof that the drug is unsafe. See Commissioner's Decision on DES, 44 FR 54852, 54861 (September 21, 1979), *aff'd, Rhone-Poulenc, Inc., Hess & Clark Div.* v. *FDA,* 636 F.2d 750 (D.C. Cir. 1980). Thus, if the agency believed that a new inactive ingredient was potentially dangerous but lacked proof that it was unsafe, and if section 505(j)(3)(H) of the act required proof that it was unsafe before it could disapprove the application, the agency would be required to approve the ANDA and then immediately initiate a proceeding to withdraw it.

The Supreme Court has held that in interpreting the Federal Food, Drug, and Cosmetic Act, the act 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. It would be inconsistent with these

principles to interpret section 505(j)(3)(H) of the act as requiring either (1) a burden of proof on the agency that would allow approval of potentially unsafe drugs, or (2) a greater showing of unsafety to disapprove a drug than is required to withdraw it. Therefore, FDA proposes to harmonize section 505(j)(3)(H) of the act with other provisions of the act and therefore interprets 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.

FDA is proposing to implement this interpretation in proposed § 314.127(h). That section provides that FDA will disapprove an ANDA if its inactive ingredients or composition raise serious questions of safety and cites examples of changes in inactive ingredients that FDA will consider to raise such serious questions. The examples reflect FDA's experience with types of changes in inactive ingredients that can adversely affect a drug's safety. The examples are not intended to be exhaustive, however, and FDA may conclude, on the basis of its experience or other information, that other types of changes raise serious questions about the safety of a drug. FDA solicits comments on additional types of changes in inactive ingredients and composition which create a reasonable basis from which to infer serious questions as to the drug's safety.

The agency lists in the regulations at proposed § 314.127(h)(2) examples of the types of changes in inactive ingredients that FDA will consider to raise serious questions about the safety of a drug product. In addition, for drug products intended for parenteral, ophthalmic, or optic use, the regulations identify the categories of added substances in which variations are not permitted and those in which variations may be permitted if the applicant demonstrates that the variation will not affect the safety of the product. (See discussion at part V section D.1.h.)

2. *Withdrawal or suspension of listed drug.* Section 505(j) of the act allows approval of ANDA's that refer to previously approved drugs, i.e., "listed drugs" within the meaning of 505(j)(2)(A)(i) and (6) of the act. The policy of allowing approval of generic copies of previously approved drugs would present significant problems if that policy allowed approval of generic copies of drugs whose approval had been withdrawn by FDA or that had been voluntarily withdrawn from sale for safety or effectiveness reasons. The statute seeks to assure that that will not happen by providing, in section 505(j)(6)(C) of the act, that a drug will be removed from listing, thus prohibiting approval of generic copies of that drug, if either of the above conditions occurs. In addition, section 505(j)(3)(I) bars the agency from approving an ANDA, even if the drug it refers to is still "listed, if there has been published a notice of opportunity for hearing on the withdrawal of approval of that listed drug. Section 505(j)(5) of the act, moreover, authorizes FDA to remove from the market, by withdrawal or suspension of approval, any generic copies already approved if the listed drug is removed from the market by FDA withdrawal or suspension of approval or is voluntarily withdrawn from sale for what the agency determines are safety or effectiveness reasons.

To assure that the intent of section 505(j)(3)(I) of the act is not evaded, the agency proposes to interpret this section broadly. Thus, § 314.162(a)(1) of the proposed rules is designed to deal with the following sequence of events: Drug A is approved under a full new drug application. Drug B is approved under an ANDA, and Drug A is the listed drug upon which it relies. The agency issues a notice of opportunity for hearing on withdrawal of approval of Drug A. Approval of Drug B will be withdrawn, in accordance with procedures discussed below, at the same time as that of Drug A. Section 505(j)(3)(I) of the act, by its terms, would prevent approval of an ANDA for Drug C that refers to Drug A as its listed drug after the notice of opportunity for hearing issues. Logically, that section should also prohibit approval of Drug C if it refers to Drug B as its listed drug, and the proposed regulation interprets the statutory language to produce that result.

A notice of opportunity for hearing is published only if the "listed" drug is being withdrawn under sections 505(e) or 505(j)(5) of the act. A drug must also be removed from the list when the agency determines that it has been voluntarily withdrawn from sale for safety or effectiveness reasons. To fulfill Congress' intent that new drugs not be approved pending the removal of a drug from the list, the agency will also refuse to approve an ANDA if the "listed" drug referred to in the ANDA was voluntarily withdrawn from sale and the agency has not determined that the withdrawal was not for safety or effectiveness reasons. (See proposed §§ 314.122 and 314.127(k).)

Where the listed drug is approved for more than one indication and the notice of proposed withdrawal proposes withdrawal of less than all of the approved indications, FDA will not approve an ANDA that includes an indication covered by the notice unless the applicant amends its ANDA with respect to labeling to remove the indication. Proposed § 314.127(i) would not apply if the ANDA seeks approval of the remaining indications only.

3. *Other grounds for disapproval.* Finally, FDA is authorized to disapprove an ANDA if the ANDA does not meet any other requirement of section 505(j)(2)(A) of the act, for example, does not contain the certifications regarding patents required in section 505(j)(2)(A)(vii) of the act, or the ANDA contains any untrue statement of material fact.

The agency proposes to add new § 314.127 to the regulations codifying the statutory reasons for disapproving an ANDA and to revise § 314.120 to state the administrative procedure governing this agency action. Under proposed revised § 314.120, if the agency concludes that there are grounds for denying approval of the ANDA, it will send the applicant a not approvable letter describing the deficiencies in the ANDA. The applicant must then either (1) withdraw its ANDA, (2) amend the ANDA incorporating already reviewed materials together with new information intended to correct all deficiencies identified in the not approvable letter, or (3) 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 ANDA under section 505(j) of the act.

The regulations describing notices of opportunity for hearing on proposals to refuse to approve applications and abbreviated applications are set forth at § 314.200. The agency proposes to make editorial, but not substantive changes in these regulations. FDA will give an applicant written notice of opportunity for hearing on its refusal to approve an ANDA if the applicant asks the agency to provide it an opportunity for a hearing. The notice of opportunity for a hearing on a refusal to approve an ANDA would generally provide, as such notices now do, a detailed description and analysis of the specific facts resulting in the agency s refusal to approve the ANDA and would refer to specific requirements in the act and regulations under which the agency refused to approve the ANDA. An applicant would have, as it now does

under § 314.200, 30 days to respond to such notice. If the applicant requests a hearing, the hearing must begin not later than 90 days after the expiration of the 30-day period, unless both the agency and the applicant agree to a later date.

N. Withdrawal or Suspension of Approval of ANDA's

ANDA's may be withdrawn or suspended under two separate sections of the act. An ANDA may be withdrawn under section 505(e) of the act, on the same grounds that a full new drug application (NDA) may be withdrawn, or an ANDA may be withdrawn or suspended under section 505(j)(5) of the act, if a listed drug on which the approval of the ANDA depends is withdrawn or suspended by FDA or voluntarily withdrawn from sale for safety or effectiveness reasons. The agency proposes to retain its current regulations under § 314.150 stating the grounds for the withdrawal of approval of applications and abbreviated applications for new drugs under section 505(e) of the act. The agency proposes to add §§ 314.151 and 314.153, however, to describe the additional circumstances under which the agency will suspend or withdraw ANDA approval under section 505(j)(5) of the act.

The procedures to be followed when NDA's and ANDA's are withdrawn under section 505(e) of the act are specified by statute. Congress was silent, however, about the procedural requirements for the withdrawal or suspension of ANDA's under section 505(j)(5) of the act. The agency therefore proposes to establish procedures that will satisfy the requirements of due process.

Section 505(e) of the act requires the Secretary to provide "due notice and opportunity for hearing" when the agency proposes to withdraw approval of an NDA or an ANDA for grounds enumerated in that section. To satisfy this requirement, the agency currently affords an opportunity for a formal evidentiary hearing under 21 CFR Part 12 when it proposes to withdraw an NDA or an ANDA under section 505(e) of the act. FDA has tentatively concluded that different procedural safeguards are due an ANDA holder under section 505(j)(5) of the act than are due an NDA holder under section 505(e) of the act, for the reasons described below.

An ANDA for a generic drug exists legally and factually only by virtue of duplicating a previously approved listed drug. The investment in gaining approval of an ANDA is generally substantially less than the investment in gaining approval of an NDA. Unlike a full new drug application, an ANDA is not required to contain evidence of the safety and effectiveness of the drug entity for its intended use. Rather, the ANDA applicant relies on a prior agency finding of safety and effectiveness for approval. That prior agency finding is dependent on the evidence presented in a previously approved new drug application. The property rights and privileges that attach to an ANDA are therefore dependent and contingent upon the validity of the innovator drug manufacturer's NDA. Under the statutory scheme, an ANDA holder has no expectation of the continued marketing of its approved drug if approval of the underlying application for the reference drug is withdrawn or suspended. Accordingly, the agency concludes that the constitutionally protected interest of an ANDA holder is different than that of an NDA holder.

The agency recognizes, however, that ANDA holders may be entitled to more extensive procedural protections when the agency proposes to withdraw approval of their applications under sections 505(e) of the act rather than under 505(j)(5) of the act. This result is procedurally fair because of the different types of issues to be resolved under the two sections of the act. When the agency proposes to withdraw an ANDA under section 505(e) of the act, rather than section 505(j)(5) of the act, the basis for withdrawal will directly concern aspects of safety and effectiveness, labeling, or manufacturing that are specific to the ANDA holder's product; the basis for such a withdrawal will not be the safety and effectiveness of the underlying drug substance. In a 505(e) proceeding that concerns only a specific ANDA and not the underlying drug substance, therefore, the ANDA holder will be in the best position to present relevant evidence and to represent its interests. In many instances, an ANDA holder alone will possess the information essential to resolving factual issues necessary for the agency to make an informed judgment about whether or not approval of the application should be withdrawn or suspended for grounds specified under section 505(e) of the act.

In 505(j)(5) proceedings, on the other hand, the basis for the agency's decision to withdraw a reference listed drug will generally only indirectly concern the ANDA holder's product. Rather, the withdrawal will be based on the safety and effectiveness of the listed drug on which the ANDA approval depends. The issues in such a proceeding will usually involve the underlying safety and effectiveness data that supported the approval of the original full new drug application. For this reason, in 505(j)(5) withdrawal proceedings, an ANDA holder will not be uniquely able to present relevant evidence.

FDA notes that Congress did not amend section 505(e) of the act to require that ANDA holders be given an opportunity for hearing when the agency proposes to withdraw the listed drug to which the ANDA referred. Instead, Congress added new section 505(j)(5) of the act, which provides for the withdrawal or suspension of an ANDA when the approval of the listed drug on which the ANDA depends, is withdrawn or suspended. The agency believes this adds weight to its interpretation that ANDA's approved under section 505(j) of the act have different rights with respect to withdrawal proceedings. Section 505(j)(5) of the act does not require an opportunity for hearing.

1. *Type of hearing to be provided.* The agency has concluded that for withdrawals of ANDA approvals under section 505(j)(5), an opportunity for an oral hearing is not required. Where no hearing of any kind is required by statute, the agency believes procedural fairness requires adequate notice of the agency's position and an opportunity to respond to the agency's contentions, before a final determination. *Aeron Marine Shipping Co.* v. *United States,* 525 F Supp. 527 535 (D.D.C. 1981), *aff'd,* 695 F.2d 567 (D.C. Cir. 1982). Many courts, applying the Supreme Court's balancing test in *Mathews* v. *Eldridge,* 424 U.S. 319, 334–35 (1976), have held "paper hearing" procedures adequate where, in the total context of the process, they are deemed to ensure adequate notice and a genuine opportunity to explain one s case. See, e.g., *Carson Products* v. *Califano,* 594 F.2d 453, 459 (5th Cir. 1979); *Basciano* v. *Herkimer,* 605 F.2d 605 (2nd Cir. 1978), *cert. denied,* 442 U.S. 929 (1979); *Zotos Internat,l, Inc.* v. *Kennedy,* 460 F Supp. 268, 279 (D.D.C. 1978), following remand to agency, No. 82–1480 (D.D.C. August 14, 1986), *aff'g* Magis. Op. (filed August 21, 1985) (upholding FDA's written procedures for contesting agency determinations of trade secret status of certain ingredients). (See also *Geneva Towers Tenants Org.* v. *Federated Mortgage Investors,* 504 F.2d 483 (9th Cir. 1974).)

The agency has concluded that an oral hearing is not necessary to satisfy the requirements of due process for withdrawal or suspension of ANDA s under section 505(j)(5) of the act. As discussed above, the interests at stake and the nature of the issues to be resolved do not demand trial-type proceedings. Accordingly, the agency

intends to provide written due process safeguards that assure adequate notice, accurate fact-finding, and an opportunity to respond to agency findings.

Nevertheless, if the agency finds that there are dispositive factual issues about the reasons for the withdrawal of the listed drug that it cannot resolve on the basis of the written submissions alone, it will provide for a limited, informal oral hearing. The discretion to hold this hearing lies exclusively with the agency. The agency generally will not provide for an oral hearing unless it cannot make an informed determination without assessing the credibility and veracity of the witnesses.

The specific procedures afforded an ANDA holder under section 505(j)(5) of the act will depend on whether the ANDA is being withdrawn or suspended because (1) the listed drug referred to in the ANDA is being withdrawn or suspended by the agency for grounds described in the first sentence of section 505(e) of the act or under section 505(j)(5) of the act or (2) the manufacturer of the listed drug has voluntarily withdrawn its drug from sale for safety or effectiveness reasons. Section N.3. and 4. below discusses the procedures provided in each case.

2. *ANDA's subject to withdrawal or suspension.* Section 505(j)(5) of the act requires that the agency withdraw or suspend a drug approved under section 505(j) of the act that "refers in its application" to a listed drug that has been withdrawn or suspended by the agency or voluntarily withdrawn by its own manufacturer for safety or effectiveness reasons. Thus, the statute might be read to permit a withdrawal or suspension under section 505(j)(5) of the act only of generic drug A, which referred in its application to the listed drug, but not of generic drug B, which referred in its application to generic drug A. If this reading were correct, section 505(j)(5) would require the agency, following the withdrawal or suspension of generic drug A, to conduct a subsequent proceeding to withdraw or suspend generic drug B.

To avoid a series of repetitive proceedings, the agency proposes to include in a single proceeding under section 505(j)(5) of the act all applications for drug products that refer to any drug that would be withdrawn or suspended under section 505(j)(5) of the act, either immediately or sequentially, as a result of the withdrawal or suspension of the listed drug. Thus, if generic drug A refers in its application to the listed drug, generic drug B refers to drug A, and generic drug C refers to generic drug B, FDA will notify the manufacturers of drugs A, B, and C that it is proposing to withdraw or suspend their approvals and give each the opportunity to participate in a single proceeding, in accordance with the terms of either § 314.151 or § 314.153. (See section N.3. and 4. below.) It should be noted, however, that cases of generic drugs sequentially referring to different listed drugs are unlikely, because in most cases the agency would require all generic applicants to refer to a single listed drug to assure uniform labeling and bioequivalence continuity.

If, as a result of this policy, a large number of manufacturers elect to participate as nonparty participants in any hearing held under 21 CFR Part 12, the presiding officer is authorized to exclude repetitive submissions. (See 21 CFR 12.94.)

The agency notes that prospective ANDA applicants, i.e., persons without approved ANDA's, have no constitutionally protected interest in whether the pioneer drug remains on the list of approved drugs and thus are not entitled to participate in the decisionmaking process concerning withdrawal or removal of a drug from "listed" status.

3. *Withdrawal of approval of an ANDA when the listed drug is withdrawn for grounds described in section 505(e)(1) through (5) of the act.* If the agency proposes to withdraw a listed drug for grounds enumerated in the first sentence of section 505(e) of the act, the listed drug's manufacturer has a right to notice and an opportunity for a formal evidentiary hearing on the withdrawal of approval of the listed drug. Except for persons subject to notice and an opportunity for a hearing under 21 CFR 310.6, the holder of an abbreviated application that is dependent on the approval of the listed drug does not have an independent right to hearing. Such an ANDA holder may, however, submit written comments on the notice of opportunity for hearing issued on the proposed withdrawal of the listed drug. The agency recognizes that there may be rare cases in which the reason for the withdrawal of the listed drug product is not applicable to the ANDA holder's drug product. For example, a withdrawal caused by a problem related to a particular dosage form might not be relevant to the safety and effectiveness of a generic version of the drug which was marketed in a different dosage form, pursuant to an approved petition under section 505(j)(2)(C) of the act. In such a case, the burden would be on the ANDA holder to submit information establishing to the agency's satisfaction the inapplicability to the generic drug product of the grounds for withdrawal.

If a hearing is granted, any ANDA holder that submitted comments on the notice of opportunity for hearing may participate in the hearing as a nonparty participant as provided for in 21 CFR 12.89. (See proposed § 314.151.) If the listed drug is withdrawn without a hearing, any ANDA's whose holders did not submit comments will be withdrawn at the same time as the listed drug. If a hearing is requested but denied, each ANDA listed in the notice of opportunity for hearing will be withdrawn at the same time as the listed drug, unless the agency determines, pursuant to proposed § 314.151(d), that the grounds for withdrawal are not applicable to a specific ANDA.

If an affected ANDA holder that has commented on the notice of opportunity for hearing does not have an opportunity to participate in a 21 CFR Part 12 hearing because a hearing is not requested, or is settled, the ANDA holder will be provided the "paper hearing" procedures set forth in proposed § 314.151. If the drug has been suspended pursuant to § 314.153 (see discussion at section N.4. below), a hearing will be provided after the drug has been removed from the market. The published notice of opportunity for hearing on the withdrawal of the listed drug will serve as the written notice detailing the reasons for the proposed withdrawal of approval of affected ANDA's and providing a summary of the evidence that the agency considers most relevant.

ANDA holders will have had an opportunity, as described above, to comment on the agency's proposed withdrawal of the drug from "listed" status. An ANDA holder should submit evidence that directly challenges the accuracy of the information considered by the agency as well as the correctness of the agency's conclusions.

Any comments received will be considered by the agency. Where no 21 CFR Part 12 hearing is held, an initial decision on the withdrawal of the listed drug and related ANDA's, which responds to significant comments, will be sent to each ANDA holder that submitted comments. These ANDA holders will then have 30 days in which to object to the agency's initial determination, in the form of a written rebuttal. If necessary to resolve dispositive factual issues, the agency may, at its discretion, hold a limited informal oral hearing. If there are no objections to the initial decision, it will become final at the expiration of 30 days from the date of its issuance. If there are

objections to the initial decision, the written rebuttals will be reviewed and responded to in the final decision.

The Director will publish a notice announcing the availability of the final decision in the **Federal Register.** If the final decision withdraws approval of the listed drug, the published notice will also (1) remove the reference drug from the list and (2) withdraw approval of and remove from the list all ANDA's identified in the notice of opportunity for hearing. See proposed §§ 314.152 and 314.162.

4. *Suspension of approval of an ANDA when the "listed" drug is voluntarily withdrawn from sale for safety or effectiveness reasons.* When the agency proposes to suspend an ANDA because it determines that the listed drug on which the ANDA's approval depends was voluntarily withdrawn from sale by the manufacturer for safety or effectiveness reasons, the ANDA holder will have an opportunity to show that the withdrawal was not for safety or effectiveness reasons or that the reasons for the withdrawal are not applicable to the generic drug. By "voluntary withdrawal, the agency means any withdrawal from sale other than a withdrawal ordered under section 505(e) or 505(j)(5) of the act. A "paper hearing" procedure will be afforded affected ANDA holders for this purpose. (See proposed § 314.153.) If the drug has been suspended pursuant to § 314.153, a hearing will be provided after the drug has been removed from the market.

If a listed drug is voluntarily withdrawn from sale and the agency determines that the withdrawal from sale was for safety or effectiveness reasons, each affected ANDA holder will be sent a copy of the agency's initial decision setting forth the reasons for its determination and its intention to remove the listed drug from the list and suspend approval of the identified ANDA's. For a discussion of the factors the agency will consider in making this determination, see section O., *infra.*

ANDA holders will have 30 days from the date the initial decision is issued to present, in writing, comments on the agency's proposed decision. An ANDA holder may also submit evidence demonstrating that the reasons for the withdrawal of the listed drug are not applicable to the drug subject to the ANDA. The agency may, at its discretion, hold a limited informal oral hearing to resolve dispositive factual issues.

If no significant comments on the proposed decision are received, the initial decision will become final at the expiration of 30 days from the date the initial decision was issued. If significant comments are received, a final decision responding to them will be issued. The final decision will be in writing and will be sent to ANDA holders who submitted comments. If the final decision affirms the agency's initial decision, it will be published in the **Federal Register** and will remove the listed drug from the list and suspend approval of, and remove from the list, all ANDA's whose holders were notified of the proposed agency action. (See proposed § 314.153(b).) For a discussion of removal of drugs from the list, see section P *infra.*

The agency is using the term "suspended" rather than "withdrawn" to describe the status of ANDA's approved by reference to a listed drug that the agency determines has been voluntarily withdrawn from sale for safety or effectiveness reasons. Section 505(j)(5) of the act provides that an ANDA approval "shall be withdrawn or suspended for the period of [the listed drug's] withdrawal from sale, or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety and effectiveness reasons. The agency believes that Congress intended that ANDA approval be reinstated immediately when either of these two conditions is met. The agency therefore intends to suspend rather than withdraw approval of ANDA's because once withdrawn, ANDA approval cannot be automatically reinstated. Instead, to regain approval of a withdrawn application, the ANDA applicant would have to obtain a new approval.

Therefore, to permit reinstatement of ANDA's, the agency proposes to suspend ANDA approval rather than withdraw it when the listed drug is determined to have been voluntarily withdrawn for safety or effectiveness reasons. Accordingly, if the approval of an ANDA depends on the approval of a drug that the agency determines is voluntarily withdrawn for safety or effectiveness reasons, the ANDA's approval will be suspended, i.e., the approval will cease to be in effect, for the period specified in section 505(j)(5)(B) of the act. The agency notes that the "imminent hazard" procedures in section 505(e) of the act do not apply to suspensions under section 505(j) of the act. The authority for "imminent hazard" suspensions cannot be delegated beyond the level of the Secretary of Health and Human Services, while no such statutory limitation applies to section 505(j) suspensions. Accordingly, the agency believes that Congress intended section 505(j) suspensions to be accomplished more expeditiously than section 505(e) suspensions.

ANDA approval will be reinstated if the agency has evidence or evidence is presented in a citizen petition demonstrating that the listed drug was not withdrawn for safety or effectiveness reasons and the agency therefore relists the withdrawn drug, or if evidence is presented in a citizen petition establishing that the basis for the withdrawal of the reference drug does not apply to the generic drug (proposed § 314.161(e)).

5. *Imminent public health hazards.* If the agency determines that a drug approved under section 505 of the act presents an unacceptable hazard to the public health, approval of its new drug application may be suspended pursuant to the "imminent hazard" provision of section 505(e) of the act. The holder of an abbreviated new drug application drug whose approval rests on a listed drug that is the subject of an "imminent hazard" proceeding will be permitted to participate in the proceeding. If approval of the listed drug is suspended as an imminent hazard, the approval of ANDA's whose approval rests on the listed drug will be suspended immediately (proposed § 314.153(a)(1)).

To assure that ANDA's for all drug products affected by an imminent hazard proceeding are suspended immediately, proposed § 314.153(a)(1) provides for the suspension of any ANDA that refers in its application to a listed drug suspended under authority of section 505(e) of the act or under authority of § 314.153(a)(1). Thus, if Drug B refers to Drug A and Drug A refers to a listed drug that is suspended in an imminent hazard proceeding under 505(e) of the act, Drug A will be suspended under § 314.153(a)(1) because its reference listed drug was suspended under authority of section 505(e) and Drug B will be suspended because its reference listed drug (Drug A) was suspended under authority of § 314.153(a)(1).

The holder of an ANDA suspended because a listed drug is found to be an "imminent hazard" will also be permitted to participate as a nonparty participant in any subsequent hearing on withdrawal of approval of the listed drug, as described above in section N.3.

If a listed drug is voluntarily withdrawn from sale for safety or effectiveness reasons and the agency concludes that the drug presents an unacceptable risk to the public, the proposed regulations also provide for the immediate suspension of ANDA approval of any drug whose approval rests on the approval of the withdrawn drug (proposed § 314.153(a)(2)). As discussed in section N.4. above, the

agency does not believe that the imminent hazard provisions of section 505(e) of the act apply to suspensions under section 505(j) of the act.

O. Determination That a Listed Drug Was Withdrawn for Safety or Effectiveness Reasons

The 1984 Amendments do not specify procedures to be followed in determining whether a drug that is voluntarily withdrawn from sale by its manufacturer is withdrawn for safety or effectiveness reasons. The statute does not require that the agency make this determination for every drug that is voluntarily withdrawn from sale, nor does it specify at what point after a voluntary withdrawal such a determination can or must be made. Many drugs are withdrawn from the market every year, and it would be a needless expenditure of resources for the agency to determine the reason for each such withdrawal. The agency is therefore interpreting section 505(j)(5) of the act to permit it to determine whether a drug is withdrawn for safety or effectiveness reasons at any time after it has ceased to be marketed.

The agency anticipates that a determination of the reasons for withdrawal of a listed drug will generally be made either when there are existing approved ANDA's that depend upon the approval of the listed drug, see § 314.153(b), when an ANDA applicant seeks to refer to a listed drug that has been voluntarily withdrawn from sale, see proposed § 314.122, or when an interested person petitions for a determination under §§ 10.25 and 10.30. The agency may, however, also make the determination at any other time on its own initiative. (See proposed § 314.161.)

The agency may determine whether a listed drug was withdrawn from sale for safety or effectiveness reasons, as required by section 505(j)(5) of the act, by attempting to focus on the intent of its manufacturer. Often, however, there will be more than one reason for the withdrawal of a drug from market by the manufacturer. Withdrawals are often accompanied by statements from the drug s manufacturer that the firm continues to have confidence in the safety and effectiveness of the product but is acting for business purposes. Drug manufacturers have also sometimes stated that the product was withdrawn from the market due to unwarranted product liability.

Because Congress did not provide the agency with subpoena power to call as witnesses the persons who made the decision to withdraw a product from sale, Congress cannot have expected the agency to discern the actual intent of the decisionmakers by direct evidence. The legislative history of this provision does make clear, however, Congress' intent that the agency examine whether the manufacturer had safety or effectiveness concerns about the withdrawn drug independent of the reasons given by the manufacturer for the withdrawal. (H. Rept. 857 Part I, at 30.) Congress, therefore, must have expected the agency to rely upon circumstantial evidence and logical inference to determine the actual intent of those who decided to withdraw the product from the market. The agency's inquiry, therefore, will focus on whether there were sufficient concerns about safety and effectiveness to make a withdrawal from sale likely and reasonable.

A determination on this issue by the agency will be based in part on the assumption that a pharmaceutical manufacturer would not cease distribution of a profitable drug if safety or effectiveness concerns had not arisen. If the withdrawn drug accounted for significant sales of the company withdrawing it, in the absence of convincing evidence to the contrary, that would be persuasive evidence that safety or effectiveness concerns prompted the manufacturer to withdraw the drug from sale. As a means of implementing the statute, the agency may establish the following rebuttable presumption. 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. FDA seeks comments on a sales figure or other methodology that would be appropriate to establish this presumption.

The agency will also consider other factors in determining whether a market withdrawal was for safety and effectiveness reasons, such as increases in the number of adverse drug reactions reported on the drug and published or unpublished studies of the drug questioning its safety or effectiveness.

If the agency makes a final decision, pursuant to § 314.153(b) or § 314.161, determining that a listed drug is withdrawn for safety or effectiveness reasons, the agency will publish a notice of the determination in the **Federal Register** (proposed § 314.161). The notice will also serve to remove the drug from the list (proposed § 314.162).

At any time after a drug is removed from the list under proposed § 314.162(a)(2), the drug may be relisted if the agency determines that the drug was not withdrawn for safety or effectiveness reasons. The agency may make this determination on its own initiative or in response to a petition submitted under §§ 10.25(a) and 10.30. If the agency decides on the basis of evidence before it that the drug was not withdrawn for safety or effectiveness reasons, it will publish a notice in the **Federal Register** announcing its determination. (See proposed § 314.161(e).) The notice will announce that the drug is relisted and serve to reinstate approval of ANDA's that were suspended when the agency published its final decision removing the listed drug from the list.

1. *Submitting an application or a suitability petition that refer to a listed drug that is no longer marketed.* Because there are many instances each year in which a drug company decides not to continue selling a drug, FDA normally will not determine whether the drug was withdrawn for safety or effectiveness reasons simply because it learns that the product was voluntarily withdrawn from sale. To assure that generic versions of unsafe or ineffective drugs do not remain on the market, the agency will, however, promptly determine the reasons for the withdrawal of a listed drug if the agency has approved ANDA's that referred to the listed drug. The agency will require persons who wish to submit ANDA's for those listed drugs that have been withdrawn from sale and for which no ANDA's have been approved or who wish to submit suitability petitions that rely on those listed drugs to show that the withdrawals from sale were not for safety or effectiveness reasons. For purposes of sections 505(j)(5) and 505(j)(6)(C) of the act, a drug shall be considered to have been "withdrawn from sale" if the applicant has ceased its own distribution of the drug, whether or not it has ordered recall of previously distributed lots of the drug. A routine, temporary interruption in the supply of a drug product would not be considered a withdrawal from sale, however, unless triggered by safety or effectiveness concerns.

Persons who wish to submit an ANDA or a suitability petition that relies on a listed drug that has been voluntarily withdrawn from the market must petition the agency with supporting documentation that the withdrawal from sale was not for safety or effectiveness reasons (proposed § 314.122). If the agency receives an ANDA or a suitability petition for such a drug unaccompanied by a petition with supporting documentation, it will refuse to approve the ANDA or suitability

petition until it can determine that the listed drug is not withdrawn for safety or effectiveness reasons (proposed §§ 314.93(e)(v) and 314.127(k)).

2. *Informing FDA of withdrawals.* The agency proposes to require holders of approved applications to notify FDA in writing when commercial distribution of a drug has been discontinued. Section 510(j)(2)(B) of the act requires the reporting of this information to FDA semi-annually as part of updating drug listing information. However, section 505(j)(6)(C) of the act requires FDA to remove a drug from the list immediately if the drug has been withdrawn from sale for safety or effectiveness reasons. Under current regulations, a manufacturer that has voluntarily withdrawn a drug from sale may, at its discretion, report the information when the discontinuance occurs (§ 207.30).

To permit FDA to satisfy its obligations under 505(j)(6)(C) of the act and to assure that ANDA's will not be approved for generic copies of listed drugs that have been voluntarily withdrawn from sale for safety or effectiveness reasons, the agency is proposing to revise § 314.81 to require the applicant to tell the agency as soon as commercial distribution of a listed drug ceases, other than for temporary interruptions in the supply of the drug. The proposed revision would require an applicant to submit to FDA on Form FDA-2657 (Drug Product Listing) a report whenever the applicant discontinues commercial marketing of an approved drug, other than for routine, temporary interruptions in the supply of the drug not caused by safety or effectiveness concerns. The report would have to be submitted within 15 working days of the discontinuance and include the following information: (1) the National Drug Code (NDC) number; (2) the identity of the drug product by established name and any proprietary name; (3) the new drug application (NDA) or abbreviated new drug application (ANDA) number; and (4) the date of discontinuance. The applicant may state the reason for its decision to withdraw the drug from sale. The proposed regulation would require the report to be submitted to the Drug Listing Branch (HFD-315), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857

P Removing Drugs from the List

Section 505(j)(6)(C) of the act requires that FDA remove from the list any drug that was withdrawn or suspended for grounds described in the first sentence of section 505(e) or in section 505(j)(5) of the act, or that the agency determines was voluntarily withdrawn for safety or effectiveness reasons. The statute requires that removal occur immediately after the agency orders suspension or withdrawal or upon the agency's determination that the drug was voluntarily withdrawn for safety or effectiveness reasons. The only procedural requirement imposed by the statute is that the agency publish a notice in the **Federal Register** announcing the removal.

The agency is proposing to combine the procedures for removal of drugs from the list with the procedures already in place for the withdrawal and suspension of listed drugs, and for a determination of the reasons for a voluntary withdrawal. The publication in the **Federal Register** of the agency's final decision withdrawing or suspending a listed drug, or of the agency's decision determining that the drug was voluntarily withdrawn for safety or effectiveness reasons will also announce the removal of the drug from the list (proposed §§ 314.152, 314.153(b)(5), and 314.161).

Q. Patent Information in Full New Drug Applications and Supplements

1. *Introduction.* Sections 505(b)(1) and 505(c)(2) of the act require that an NDA applicant "file with its application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. This provision requires that an applicant submit information about any patent that meets the statutory description whether or not the applicant owns or is licensed under such a patent. Required patent information must be submitted with all original applications submitted under section 505(b) of the act, including applications described in section 505(b)(2) of the act and with certain supplemental applications. Upon approval of the application, the statute requires that FDA publish patent information submitted under section 505(b) of the act. Patent information on unapproved products or on patents beyond the scope of the act (i.e., process patents) will not be published. Proposed new § 314.53 would contain the regulations implementing the statutory provision requiring the submission of patent information. FDA also proposes to revise § 314.50 by designating paragraph (h) as paragraph (k) and adding a new paragraph (h) that would refer to the requirements of proposed new § 314.53.

2. *Patents for which information must be submitted.* The patents that FDA regards as covered by this statutory provision are those that claim the drug (active ingredient or ingredients) or drug product, and use patents for a particular indication or method of using the product. The agency has concluded that formulation and composition patents are drug product patents within the meaning of this statutory provision about which information must be submitted to and published by FDA. Process patents (patents that claim a method of manufacturing) are not covered by the statute and information on these patents are not to be submitted and will not be published by FDA.

The agency will not accept patent information that pre-dates an official notice by the United States Patent and Trademark Office that a patent has been granted. Thus, an applicant should not anticipate the granting of a patent. The applicant may informally notify the agency of an impending patent, but no official action will be taken in response to such notice.

3. *Reporting requirements.* The agency proposes in § 314.53(c) that each required submission of patent information contain the patent number, the date on which the patent will expire, a statement as to whether the patent is a drug patent, drug product patent, or use patent, and the name of the patent owner. Identifying the type of patent will assist the agency in assuring that those types of patents that require a certification by a generic applicant have such certification and that use patents are clearly identified for publishing in the list. Under this proposal, if the patent owner or applicant does not reside or have a place of business in the United States, the application would be required to include the name of an agent (representative) of the patent owner or applicant who resides or maintains a place of business within the United States authorized to receive notice of patent certification under sections 505(b)(3) and 505(j)(2)(B) of the act.

As noted above, information will be published in the list only on patents that claim approved drug products or that claim approved indications or other conditions of use. Therefore, to assist the agency in ensuring that only appropriate patents are published for patents that claim a drug, drug product, or method of use an applicant would submit information only on those patents that claim an approved drug product or approved method of using such drug product, or drug product or a

method of using such drug or drug product for which the applicant has submitted an application to obtain FDA approval. The patent information for each formulation or composition (drug product) patent would be required to include the following certification:

The undersigned certifies that the drug and the formulation or composition of (*name of drug product*) is claimed by Patent No. _____. This product is (*currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act*) [*or*] (*the subject of this application for which approval is being sought*).

Under the proposal, an applicant would, before approval of the application, submit a certification for each formulation or composition patent that claimed the drug product for which the applicant was seeking approval. Because formulations are often changed during the approval process, within 30 days after the date of approval of the application, if the original application submission included a certification about a formulation or composition patent, the applicant would be required to submit an amended certification identifying the patents that claim the approved formulation or composition of the drug product. If an approved formulation is changed by an applicant through the submission and approval of a supplemental application and an existing formulation patent no longer claims the new approved formulation, the new drug application holder must notify FDA so that the patent can be removed from the list. Similarly, FDA should be notified if a patent holder no longer intends to enforce a patent, for example, because the patent is no longer valid. This will assist the agency in maintaining accurate patent information in its list and generic applicants in complying with the patent certification requirements under sections 505(b)(2) and 505(j) of the act.

With respect to a use patent, the agency proposes to require an applicant to submit a certification that identifies each patent that claims indications or conditions of use that are approved or are the subject of the application for which the applicant is seeking approval. Because all indications or conditions of use for which an applicant sought approval may not be approved, within 30 days after the date of approval of the application; if the original application submission included a certification about a method of use patent, the applicant would be required to submit an amended certification identifying the approved indications or conditions of use and the patents that claim those uses. The purpose of this requirement is to provide some guidance to applicants required to submit either a patent certification under section 505(b)(2)(A) or 505(j)(2)(A)(vii) or a statement under section 505(b)(2)(B) or 505(j)(2)(A)(viii) of the act (proposed § 314.94(a)(12)). When a generic applicant concludes that a use patent does not claim the use for which the applicant seeks approval, the applicant is required only to submit a statement under section 505(b)(2)(B) or 505(j)(2)(A)(viii) so stating to FDA. The applicant is not required to notify the patent owner of the applicant's intent to market a copy of the patented drug. If the patent owner does not specify which approved indications or conditions of use are covered by its patent, the generic applicant may interpret the scope of the patent more narrowly than would the patent owner, thereby avoiding the certification and notification provisions of the statute.

FDA's experience implementing the patent certification provisions suggests that where the patent owner and generic applicant disagree as to the applicability of a use patent, the patent owner may seek to have FDA intervene, by alleging that the generic applicant has not complied with the patent certification and notification provisions of the act. Because FDA has no expertise in the field of patents, the agency has no basis for determining whether a use patent covers the use sought by the generic applicant. Nor does FDA believe that Congress intended the patent provisions of Title I of the 1984 Amendments to require the agency to make such determinations. On the contrary, the 1984 Amendments are plainly structured to allow any patent disputes to be litigated in federal court. To ensure that FDA is not required to determine the scope of a use patent, the agency can either require the applicant to make a certification as to the covered approved indications and require generic applicants to file patent certifications as to those indications, or the agency can allow the generic applicant complete discretion to interpret the scope of any relevant use patent. The agency believes that the first approach more fairly implements Congress' intent that patent owners receive preapproval notice of potentially infringing products.

FDA therefore proposes that after approval of an application submitted under section 505 of the act that contained a certification that a method of use patent covered an indication for which the applicant sought approval, the applicant would be required to amend its certification to identify the specific indications or conditions of use that have been approved and the patents that claim those uses. If the applicant is not the patent owner, the applicant should obtain this amended certification from the patent owner, because the applicant has the responsibility for providing FDA with the required patent information. Upon approval of an application, the agency will publish in the list all use patents that claim an approved indication and for each patent identify the approved indications or conditions of use covered by the patent.

The proposal also would require that if an applicant believes that there are no patents that claim the drug or drug product, nor that claim an approved method of using the drug product and with respect 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, the applicant would include in its application a certification stating this belief.

Finally, under proposed § 314.53, a certification required under the section must be signed by the applicant or patent owner, or the applicant's or patent owner's attorney, agent (representative), or other authorized official.

4. *When and where to submit patent information.* If a patent is issued on a drug or drug product or on a method of using a drug product before an application is filed with FDA, information on the patent must be submitted with the application. If a patent is issued after an application is filed with FDA but before the application is approved, the applicant must submit the required patent information in an amendment to the application under § 314.60. If a patent is issued after the application has been approved, the applicant must submit the required patent information by letter within 30 days of the date of issuance of the patent.

The act and proposed regulations contemplate amendment of an application when a patent is issued after submission, and before approval, of a full application. If a patent has not been submitted to FDA by the time FDA determines that an abbreviated new drug application or a 505(b)(2) application can be approved, and the generic applicant certifies that it is unaware of any relevant patents, the agency will not delay approval of the application. If the holder of a new drug application submits patent information after the application for the generic drug has already been approved, FDA will not attempt to rescind or withdraw approval.

Holders of or applicants for ANDA s or 505(b)(2) applications who are

licensed under a patent are encouraged to submit information concerning the patent license so that information on the patent can be listed with their products as well as with the patent owner's product, thus assuring that the patent protection features of the act are preserved for that patent. Licensees are also required to submit information concerning a patent licensing agreement if they wish to avoid a delayed effective date. (See proposed § 314.107(b)(1).)

In general, supplements are subject to the same patent submission requirements as original applications. Many supplements, however, are for changes that could not be patented. Rather than require patent submissions for every supplement, the agency proposes to require that patent information be submitted only for the following types of changes for which applicants must submit supplements: (1) changes in formulation; (2) new indications or other conditions of use, including a change in route of administration; (3) changes in strength; or (4) any other patented changes. FDA recognizes that there are formulation changes that are unpatentable and could be specifically excluded from the requirement of submitting patent information. However, FDA does not have the expertise to identify such unpatentable formulation changes. FDA solicits comments on this policy of requiring patent information only for certain supplements, and on the types of supplements for which patent information should be required.

Under the proposal, if new patents or existing patents cover the changes for which approval is sought in a supplement, the applicant would be required to submit the required patent information with the supplement. If existing patents for which information has already been submitted claim the change, the applicant would be required to submit a certification with the supplement identifying the patents that claim the change. If the applicant submits a supplement for one of the changes listed above and no patents, including previously submitted patents, claim the change, the applicant would be required to so certify. The patent information and certifications would be required to be submitted by letter separate from, but at the same time as, the supplement.

The agency proposes to require an applicant to submit two copies of each submission of patent information; an archival copy and a copy for the chemistry, manufacturing and controls section of the review copy of an application or supplement. The regulations would require the applicant to submit patent information to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, Park Bldg., Rm. 214, 12420 Parklawn Dr., Rockville, MD 20857 Each submission of patent information, except information submitted with an original application, and its mailing cover would be required to bear prominent identification as to its contents, i.e., "Patent Information" or, if submitted after approval of the application, "Time Sensitive Patent Information.

5. *Untimely submission.* PMA suggested regulatory language designed to allow a pioneer holder to update, at any time, its patent information. FDA does not believe that specific regulatory language is necessary. If patent information on a patent issued after approval of an application is not timely submitted, i.e., is submitted more than 30 days after issuance of the patent, the agency could refuse to publish in the list the untimely information, or could withdraw approval of the new drug application if its applicant failed to respond within 30 days to a notice from the agency (21 U.S.C. 355(e)(4)). FDA has concluded, however, that while Congress clearly intended to enforce timely submission, a less severe penalty for late submission would effectuate Congress' intent without eliminating all statutory patent protection or withdrawing approval of the new drug application itself. Therefore, if a new drug application applicant submits required patent information on an approved drug product more than 30 days after issuance of the patent, FDA will publish the untimely information but will not require ANDA and 505(b)(2) applicants with pending applications who have previously submitted a certification, i.e., those applicants who would be prejudiced by the late submission, to recertify as to the new patent. Only applicants who initially submit ANDA's or 505(b)(2) applications after the submission of the patent information or whose pending applications do not contain a valid certification at the time of the submission would be required to submit a certification as to that patent. (See proposed §§ 314.50(i)(4) and 314.94(a)(12)(vi).)

The date that the patent information is received by the Central Document Room will generally be considered the date the information was submitted. Determining the date on which patent information is submitted is important because ANDA and 505(b)(2) applicants are required to notify a patent owner of the submission of an application for a potentially infringing drug product only if information on the patent has been submitted to FDA before approval of the ANDA or 505(b)(2) application. If questions arise as to whether patent information has been submitted, FDA will review the archival records in the Central Document Room. If there is no evidence then that patent information has been submitted, no patent information will be considered to have been submitted.

6. *Submission errors.* In deciding whether a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug, the agency will defer to the information submitted by the NDA applicant. If any interested person disputes the accuracy or relevance of patent information submitted by an NDA applicant and published by FDA in the list, or believes that an applicant has failed to submit required patent information, that person should first notify the agency informally, stating the grounds for the disagreement by writing to the Director, Office of Drug Standard (HFD-200), 5600 Fishers Lane, Rockville, MD 20857 The agency will contact the new drug application holder requesting that the correctness of the submission or omission be confirmed. Unless the new drug application holder withdraws or changes the patent submission, the agency will not change the patent information in the list. If there is no change to the patent information in the list, a section 505(b)(2) or 505(j) application submitted for the drug must, despite any disagreement, contain a certification for each listed patent and any patent challenge must then be pursued through private legal action under the patent laws.

The agency proposes to revise §314.125 to add an additional reason for refusing to approve a new drug application. Under section 505(d)(6) of the act, the agency is obligated to refuse to approve an application if the application failed to contain the required patent information.

The agency proposes to revise § 314.150 to add an additional ground for the withdrawal of approval of a new drug application. As noted above, the statute provides that the agency is obligated to withdraw approval of an application if the application fails to contain the required patent information within 30 days after receipt of a written notice from FDA specifying the failure to provide such information. Although ordinarily the agency intends to invoke a less severe penalty for late submissions (see discussion under

section 0.5., FDA has the authority to withdraw approval of an application if an applicant has been notified of its failure to provide required patent information and the applicant does not respond within 30 days.

R. Public Disclosure of Safety and Effectiveness Data

Section 505(l) of the act specifies when safety and effectiveness data submitted as part of a new drug application are publicly disclosable. Those provisions were implemented by the agency's final rule published in the **Federal Register** of February 22, 1985 (50 FR 7452) that revised 21 CFR Part 314 governing the approval for marketing of new drugs and antibiotic drugs for human use. No changes to those provisions are being made by this proposed rule.

VI. Conforming Amendments

21 CFR 310.305 requires adverse drug experience reporting for marketed prescription drugs not the subject of approved new drug or abbreviated new drug applications. Those rules were patterned after the adverse drug experience reporting provisions under 21 CFR 314.80. To ensure consistency between these two sets of rules, the agency is proposing to revise § 310.305 to adopt changes identical to those proposed in this document for § 314.80 concerning the definition of the term "adverse drug experience" and reports on increased frequency of therapeutic failure (lack of affect).

The provisions of the 1984 Amendments with respect to bioequivalence, FDA's followup to the Bioequivalence Hearing held September 29 through October 1, 1986, and current agency policy necessitate changes in the regulations in 21 CFR Part 320.

In 21 CFR Part 320, FDA proposes to revise the table of contents to reflect the changes described below.

In § 320.1, FDA proposes to (1) revise the definition of "bioavailability" to add a reference to drugs that are not intended to be absorbed, (2) restate the definition of "bioequivalence, and (3) remove the definition of "bioequivalence requirement.

In § 320.21, FDA proposes to restate the requirements for submission of bioavailability and bioequivalence data.

In § 320.22, FDA proposes to revise paragraph (b)(1) to restate the waiver provision and to remove the automatic waiver of evidence of in vivo bioavailability for topically applied preparations (§ 320.22(b)(2)) and oral dosage forms not intended to be absorbed (§ 320.22(b)(3)) because the agency believes the in vivo bioavailability of such products should not be considered self-evident in every case. Variations in the manufacturing process (including a change in product formulation) used by each individual manufacturer may result in differences in the bioavailability of these drug products. Therefore, the agency intends to review each product on a case-by-case basis to determine if an in vivo bioavailability study is necessary.

It should be emphasized, however, that although the automatic waiver provisions under § 320.22 would no longer apply to topical drug products and oral dosage forms not intended to be absorbed, the agency may, in appropriate cases, waive the in vivo requirement.

In § 320.22(b)(4)(i) (proposed § 320.22(b)(2)), FDA proposes to delete the words "or vapor. These words have been inaccurately interpreted by applicants to apply to aerosol drug products.

In § 320.22(b)(5)(ii) (proposed § 320.22(b)(3)), FDA proposes to require that the active drug ingredient be in the same concentration and dosage form. This change conforms to current agency policy.

Current § 320.22(c)(1) states that FDA shall waive the requirement of in vivo bioavailability testing for 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 DESI notice, if the drug is not on the list of so-called "bioproblem drugs" codified in § 320.22(c)(1). The waiver embodied in this provision resulted from the DESI review. During the review, because of the need to evaluate large numbers of products in a short time and in light of FDA's long experience with these drugs, FDA developed criteria for determining whether products approved before 1962 could be found bioequivalent on the basis of in vitro rather than in vivo data. (These criteria are codified in current § 320.52, proposed § 320.32.) If, after applying the criteria, FDA determined that a drug presented an actual or potential bioequivalence problem, it was placed on the list of bioproblem drugs, and in vivo data were required for approval. Those drugs that did not present such a problem could satisfy the bioavailability/bioequivalence requirements by meeting an appropriate in vitro standard.

There is no evidence that the policy of waiver of in vivo bioavailability for those DESI oral dosage forms that do not present an actual or potential bioequivalence problem has resulted in the approval of products that are not bioequivalent. FDA has therefore concluded that there is no reason to change the policy at this time. Proposed § 320.22(d) will thus continue to provide for a waiver of in vivo studies for DESI oral dosage forms that do not present an actual or potential bioequivalence problem. The list of bioproblem drugs currently codified in the regulation, however, is no longer necessary. The 1984 Amendments provide that FDA shall publish in the list of approved drugs a statement of whether, for each drug, in vitro or in vivo studies are required to show bioequivalence. (See section 505(j)(6)(III) of the act.) FDA satisfies this requirement through the use of therapeutic equivalence codes in the list. Thus, for each DESI product (as well as for each post-1962 product), the list provides notice of FDA's determination whether the drug presents an actual or potential bioequivalence problem, requiring an in vivo study. Consequently, FDA's implementation of the requirement in section 505(j)(6)(III) of the act makes the codified list of bioproblem drugs in § 320.22(c)(2) superfluous.

In addition, the list of bioproblem drugs, which has not been amended since 1981, does not include all pre-1962 products that FDA currently believes present an actual or potential bioequivalence problem. For example, a complete list of bioproblem drugs would also include products that are "identical, related, or similar" to those products on the list (See current § 320.22(c)(1)). In addition, since 1981, the agency has publicly identified, e.g., through **Federal Register** notices, additional drug products covered by the DESI review that the agency has determined present actual or potential bioequivalence problems, and that therefore require in vivo studies.

FDA is therefore proposing to remove the list of bioproblem drugs from existing § 320.22(c)(1), and to provide notice of in vitro or in vivo study requirements for particular DESI drugs through the list. As proposed, § 320.22(d) (formerly § 320.22(c)(1)) will continue to require FDA to waive in vivo studies for those DESI oral dosage forms that FDA determines do not present an actual or potential bioequivalence problem, but those determinations will appear in the list rather than in the regulation. If FDA determines that a DESI product previously considered a nonbioproblem drug should be reclassified as a bioproblem drug, FDA will provide notice of its tentative conclusion in a monthly supplement to the list and solicit comment. After considering any comments received, FDA will make a final determination, which will be

reflected in a subsequent monthly supplement.

In § 320.22, FDA proposes to remove paragraphs (c)(3) and (d)(1) because they are no longer relevant. FDA no longer intends to establish separate bioequivalence requirements for bioproblem drug products.

In proposed § 320.22(e) (formerly § 320.22(d)), FDA proposes to revise paragraph (4) to clarify that the differences in color, flavor, or preservative could not affect the bioavailability of the reformulated product.

In proposed § 320.22(e) (formerly § 320.22(d)), FDA proposes to remove paragraph (d)(5). The agency has no evidence to show that in vitro data alone are regularly sufficient to assure bioequivalence. In vitro testing can be used for drugs where there is a known in vivo/in vitro correlation, and has been used for pre-1962 drugs not suspected of having, or not likely to have, a bioavailability problem. For all other drug products, an in vivo bioequivalence study on the product is required to support at least one strength of the product. Notice of FDA's determination whether in vivo or in vitro studies are required to show bioequivalence is published in the list.

In proposed § 320.22(f), FDA proposes to modify the provision to clarify that deferral of a requirement for the submission of evidence of in vivo bioavailability is applicable only to full new drug applications. Under the 1984 Amendments, there is no authority to defer a showing of bioequivalence for abbreviated new drug applications.

In § 320.22, FDA proposes to add new paragraph (g) to state that FDA, for good cause, may require evidence of in vivo bioavailability for any drug product if the agency determines that any difference between a proposed drug product and a listed drug may affect the bioavailabilty of the proposed drug product. For example, the generic applicant may use a manufacturing process (including a formulation change) different from that used by the manufacturer of the listed drug, a difference that may affect the proposed product's bioavailability.

In § 320.23, FDA proposes to revise the provision to refer to the statutory standard for bioequivalence.

In § 320.24, FDA proposes to state the methods that may be used to meet an in vivo or in vitro testing requirement.

In § 320.30, FDA proposes to revise the provisions to apply both to inquiries about bioavailability and bioequivalence requirements.

In § 320.31, FDA proposes to clarify when an "Investigational New Drug Application" is required for an in vivo bioavailability or bioequivalence study.

Because the 1984 Amendments impose a bioequivalence requirement on all drug products that are the subject of ANDA's, FDA no longer intends to establish separate bioequivalence requirements for bioproblem drug products. Therefore, FDA proposes to amend its regulations in 21 CFR Part 320 under Subpart C by removing the subpart heading and those regulations that apply to establishing a bioequivalence requirement, and to revise the remaining regulations to delete any reference to establishing a bioequivalence requirement. The agency proposes to retain, move to Subpart B, and redesignate § 320.52 (proposed § 320.32) *Criteria and evidence to assess actual or potential bioequivalence problems,* § 320.55 (proposed § 320.33) *Requirements for batch testing and certification by the Food and Drug Administration,* § 320.56 (proposed § 320.34) *Requirements for in vitro testing of each batch,* and § 320.62 (proposed § 320.35) *Requirements for maintenance of records of bioequivalence testing.* In addition, elsewhere in this issue of the **Federal Register**, FDA is withdrawing 11 proposed rules that would have established bioequivalence requirements for certain drug products listed under existing § 320.22(c).

VII. Economic Assessment

The agency has considered the economic impact of this rule, and the relationship of the requirements in this rule with Pub. L. 98-417 The provisions in Title I of Pub. L. 98-417 that eliminated unnecessary regulatory barriers for duplicate products have demonstrated a capacity to achieve their intended economic consequences. Generic competition has already commenced on many important post-1962 drugs. Recent public reports of generic drug sales estimate their market share at nearly 25 percent of total prescription drug sales. At least half of these generic sales may be post-1962 drugs that would not have benefited from the price savings of multisource competition without enactment of Pub. L. 98-417 Thus, this increased competition is already saving consumers hundreds of millions of dollars per year. The agency concludes that these impacts are directly attributable to the statute. This rule will not affect the pace or magnitude of these already evident economic impacts. The procedures and interpretations provided by the rule will clarify and facilitate implementation of Title I, but the rule by itself does not create a significant economic impact.

Thus, the agency 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 this 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).

VIII. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this proposed 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.

IX. Paperwork Reduction Act of 1980

This proposed rule contains information collections which are subject to review by the Office of Management and Budget (OMB) 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 contained in the proposed rule would 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
314.52	30	1	8 hours	240
314.53	200	1	1 hour	200
314.54	10	1	80 hours	800
314.80, 310.305	40	1	8 hours	320
314.81	700	1	10 minutes	119
314.93	82	1	10 hours	820
314.94	850	1	160 hours	136,000
314.95	30	1	16 hours	480
314.107	10	1	8 hours	80
314.110	10	1	40 hours	400
314.122, 314.161	1	1	10 hours	10
Total				139,586

The agency has submitted a copy of this proposed rule to OMB for its review of these information collections. Interested persons are requested to send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to, FDA's Dockets Management Branch (address above), and to the Office of Information and Regulatory Affairs, OMB, Rm. 3208, New Executive Office Bldg., Washington, DC 20503, Attn: Desk Officer for FDA.

X. Request for Comments

Interested persons may, on or before October 10, 1989, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 10

Administrative practice and procedure, News media.

21 CFR Part 310

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

21 CFR Part 314

Administrative practice and procedure, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 320

Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner, it is proposed that Parts 10, 310, 314, and 320 be amended as follows:

PART 10—ADMINISTRATIVE PRACTICES AND PROCEDURES

1. The authority citation for 21 CFR Part 10 is revised to read as follows:

Authority: Sec. 201 *et seq.*, Pub. L. 717 52 Stat. 1040 as amended (21 U.S.C. 321 *et seq.*); sec. 1 *et seq.*, Pub. L. 410, 58 Stat. 682 as amended (42 U.S.C. 201 *et seq.*); sec. 4, Pub. L. 91–513, 84 Stat. 1241 (42 U.S.C. 257a); sec. 301 *et seq.*, Pub. L. 91–513, 84 Stat. 1253 (21 U.S.C. 821 *et seq.*); sec. 409(b), Pub. L. 242, 81 Stat. 600 (21 U.S.C. 679(b)); sec. 24(b), Pub. L. 85–172, 82 Stat. 807 (21 U.S.C. 467f(b)); sec. 2 *et seq.*, Pub. L. 91–597 84 Stat. 1620 (21 U.S.C. 1031 *et seq.*); secs. 1–9, Pub. L. 625, 44 Stat. 1101–1103 as amended (21 U.S.C. 141–149); secs. 1–10, Ch. 358, 29 Stat. 604–607 as amended (21 U.S.C. 41–50); sec. 2 *et seq.*, Pub. L. 783, 44 Stat. 1406 as amended (15 U.S.C. 401 *et seq.*); sec. 1 *et seq.*, Pub. L. 89–755, 80 Stat. 1296 as amended (15 U.S.C. 1451 *et seq.*); sec. 101, Pub. L. 98–417 98 Stat. 1585 (21 U.S.C. 355).

2. 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.

3. 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

4. The authority citation for 21 CFR Part 310 continues to read as follows:

Authority: Secs. 501, 502, 503, 505, 701, 704, 705, 52 Stat. 1049–1053 as amended, 52 Stat.

1055–1056 as amended, 67 Stat. 477 as amended, 52 Stat. 1057–1058 (21 U.S.C. 351, 352, 353, 355, 371, 374, 375); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

5. 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 by removing the words "(Drug Experience Report)" and replacing them with "(Adverse Reaction Report)" in paragraph (d)(1), 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 assure 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

6. 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, and by revising the table of contents and the authority citation 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. 501, 502, 503, 505, 506, 507 701, 52 Stat. 1049–1053 as amended, 1055–1056 as amended, 98 Stat. 1585, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 353, 355, 356, 357 371); 21 CFR 5.10, 5.11.

§ 314.1 [Amended]

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

8. 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, 52 Stat. 1040 et seq., as amended (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 amendments and supplements to the application.

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 used in the synthesis of such ingredient.

"FDA means the Food and Drug Administration.

"Listed drug" means 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 not 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. A drug product is deemed to be included in the list on the date of approval of the application or abbreviated application for that drug product. For a drug product that is subject to FDA's Drug Efficacy Study Implementation (DESI) program, FDA will consider the applicable DESI notice published in the **Federal Register** a listed drug until a drug product subject to the notice meets the conditions for approval of effectiveness set forth in the notice and becomes a listed drug.

"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 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.

"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 current edition of FDA's publication Approved Drug Products with Therapeutic Equivalence Evaluations" and any current supplement to the publication.

"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) 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.

9. Section 314.50 is amended by revising the first and fifth sentences in the introductory paragraph, paragraph (a)(2), the second sentence in paragraph (c)(1), by adding new paragraph (g)(3), by redesignating existing paragraph (h) as paragraph (k), and by adding new paragraphs (h), (i), and (j) 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.

(h) *Patent information.* The application is required to contain the patent information described under § 314.53.

(i) *Patent certification*—(1) *Contents.* A 505(b)(2) application is required to contain the following:

(i) *Patents claiming drug, drug product, or method of use.* (*a*) Except as provided in paragraph (i)(2) of this section, a certification with respect to each patent issued by the United States Office of Patent and Trademark that, in the opinion of the applicant and to the best of its knowledge, claims the drug or drugs on which investigations that are relied upon by the applicant for approval of its application were conducted or that claims an approved use for such drug or drugs and for which information is required to be filed under section 505 (b) and (c) of the act and § 314.53. For each such patent, the applicant shall provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(*1*) That the patent information has not been submitted to FDA. The applicant shall entitle such a certification "Paragraph I Certification".

(*2*) That the patent has expired. The applicant shall entitle such a certification "Paragraph II Certification".

(*3*) The date on which the patent will expire. The applicant shall entitle such a

certification "Paragraph III Certification"; or

(4) That the patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. The applicant shall entitle such a certification "Paragraph IV Certification. This certification shall be submitted in the following form:

I, (*name of applicant*), certify that Patent No. (*is invalid or will not be infringed by the manufacture, use, or sale of*) (*name of proposed drug product*) for which this application is submitted.

The certification shall be accompanied by a statement that the applicant will comply with the requirements under § 314.52(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent and with the requirements under § 314.52(c) with respect to the content of the notice.

(*b*) If the drug on which investigations that are relied upon by the applicant were conducted is itself a licensed generic drug of a patented drug first approved under section 505(b) of the act, the appropriate patent certification under this section with respect to each patent that claims the first-approved patented drug or that claims an approved use for such drug.

(ii) *No relevant patents.* If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (i)(1)(i) of this section, a certification in the following form:

In the opinion and to the best knowledge of (*name of applicant*), there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

(iii) *Method of use patent.* (*a*) If information that is submitted under section 505 (b) or (c) of the act and § 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, a statement explaining that the method of use patent does not claim any of the proposed indications.

(*b*) If the labeling of the drug product for which the applicant is seeking approval includes an indication that, according to the patent information submitted under section 505 (b) or (c) of the act and § 314.53 or in the opinion of the applicant, is claimed by a use patent, the applicant shall submit an applicable certification under paragraph (i)(1)(i) of this section.

(2) *Method of manufacturing patent.* An applicant is not required to make a certification with respect to any patent that claims only a method of manufacturing the drug product for which the applicant is seeking approval.

(3) *Licensing agreements.* If a 505(b)(2) application is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, the applicant shall submit a certification under paragraph (i)(1)(i)(*a*)(*4*) of this section ("Paragraph IV Certification") as to that patent and a statement that it has been granted a patent license. If the patent owner consents to an immediate effective date upon approval of the 505(b)(2) application, the application shall contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to an immediate effective date.

(4) *Late submission of patent information.* If a patent described in paragraph (i)(1)(i)(*a*) of this section is issued and the holder of the approved application for the patented drug does not submit the required information on the patent within 30 days of issuance of the patent, an applicant who submitted a 505(b)(2) application that before the submission of the patent information contained an appropriate patent certification is not required to submit an amended certification. An applicant whose 505(b)(2) application is filed after a late submission of patent information or whose 505(b)(2) application was previously filed but did not contain an appropriate patent certification at the time of the patent submission shall submit a certification under paragraph (i)(1)(i) or (ii) or a statement under paragraph (i)(1)(iii) of this section as to that patent.

(5) *Disputed patent information.* If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under § 314.53(f). Unless the patent information is withdrawn or changed, the applicant must submit an appropriate certification for each relevant patent.

(6) *Amended certifications.* A certification submitted under paragraphs (i)(1)(i) through (iii) of this section may be amended at any time before the effective date of the approval of the application. An applicant shall submit an amended certification as an amendment to a pending application or by letter to an approved application. Once an amendment or letter for the change in certification has been submitted, the application will no longer be considered to be one containing the prior certification.

(i) *After finding of infringement.* An applicant who has submitted a certification under paragraph (i)(1)(i)(*a*)(*4*) of this section and is sued for patent infringement within 45 days of the receipt of notice sent under § 314.52, shall amend the certification if a final judgment in the action is entered finding the patent to be infringed. In the amended certification, the applicant shall certify under paragraph (i)(1)(i)(*a*)(*3*) of this section that the patent will expire on a specific date.

(ii) *After removal of a patent from the list.* If a patent is removed from the list for any reason other than because the patent has been declared invalid in a lawsuit brought within 45 days of a notice issued under § 314.52, after one or more applicants have made certifications under paragraph (i)(1)(i)(*a*)(*4*) of this section on that patent, any applicant with a pending application or delayed effective date who has made such a certification shall amend the certification. In the amended certification, the applicant shall certify under paragraph (i)(1)(ii) of this section, if applicable, that no patents described in paragraph (i)(1)(i) of this section claim the drug. If other relevant patents claim the drug, the applicant shall instead submit a request to withdraw the certification under paragraph (i)(1)(i)(*a*)(*4*) of this section.

(iii) *Other amendments.* (*a*) Except as provided in paragraphs (i)(4) and (i)(6)(iii)(*b*) of this section, an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate.

(*b*) An applicant is not required to amend a submitted certification when information on an otherwise applicable patent is submitted after the 505(b)(2) application is approved, whether or not the approval of the abbreviated application is effective.

(j) *Claimed exclusivity.* A new drug product, upon approval, may be entitled to a period of marketing exclusivity under the provisions of § 314.108. If an applicant believes its drug product is entitled to a period of exclusivity, it shall submit to the new drug application prior to approval the following information:

(1) A statement that the applicant is claiming exclusivity.

(2) A reference to the appropriate paragraph under § 314.108 that supports its claim.

(3) If the applicant claims exclusivity under § 314.108(b)(2), information to show that no drug has previously been approved under section 505(b) of the act containing any active moiety in the drug for which the applicant is seeking approval.

(4) If the applicant claims exclusivity under § 314.108(b)(4) or (5), the following information to show that the clinical investigations in its application are "new clinical investigations, "essential to approval of the application or supplement, and were "conducted or sponsored by the applicant"·

(i) "*New clinical investigations.* A certification that to the best of the applicant's knowledge the clinical investigations included in the application meet the definitions of "new" and "clinical investigations" set forth in § 314.108(a).

(ii) "*Essential to approval.*" A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which the applicant is seeking approval, a certification that the applicant has thoroughly searched the scientific literature and, to the best of the applicant's knowledge, the list is complete and accurate and, in the applicant's opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigation(s) in the application, and an explanation as to why the studies or reports are insufficient.

(iii) "*Conducted or sponsored by.* If the applicant was the sponsor named in the Form FDA–1571 for an investigational new drug (IND) under which the new clinical investigation(s) that is essential to the approval of its application was conducted, identification of the IND by number. If the applicant was not the sponsor of the IND under which the clinical investigation(s) was conducted, a certification that the applicant or its predecessor in interest provided substantial support for the clinical investigation(s) that is essential to the approval of its application, and information supporting the certification.

10. New §§ 314.52, 314.53, and 314.54 are added to Subpart B to read as follows:

§ 314.52 Notice of certification of invalidity or noninfringement of a patent.

(a) For each patent which claims the drug or drugs on which investigations that are relied upon by the applicant for approval of its application were conducted or which claims a use for such drug or drugs and which the applicant certifies under § 314.50(i)(1)(i)(*a*)(*4*) that a patent is invalid or will not be infringed, the applicant shall send notice of such certification by registered or certified mail, return receipt requested to each of the following persons:

(1) Each owner of the patent that is the subject of the certification or the representative designated by the owner to receive the notice. The name and address of the patent owner or its representative may be obtained from the United States Patent and Trademark Office; and

(2) The holder of the approved application under section 505(b) of the act for each drug product which is claimed by the patent or a use of which is claimed by the patent and for which the applicant is seeking approval, or, if the application holder does not reside or maintain a place of business within the United States, the application holder's attorney, agent, or other authorized official. The name and address of the application holder or its attorney, agent, or authorized official may be obtained from the Division of Drug Information Resources (HFD–80), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857

(3) This paragraph does not apply to a use patent that claims no uses for which the applicant is seeking approval.

(b) The applicant shall send the notice required by paragraph (a) of this section when it receives from FDA an acknowledgment letter stating that its application has been filed. At the same time, the applicant shall amend its application to include a statement certifying that the notice has been provided to each person identified under paragraph (a) of this section and that the notice met the content requirement under paragraph (c) of this section.

(c) *Content of a notice.* In the notice, the applicant shall cite section 505(b)(3)(B) of the act and shall include, but not be limited to, the following information:

(1) A statement that a 505(b)(2) application submitted by the applicant has been filed by FDA.

(2) The application number.

(3) The established name, if any, as defined in section 502(e)(3) of the act, of the proposed drug product.

(4) The active ingredient, strength, and dosage form of the proposed drug product.

(5) The patent number and expiration date, as submitted to the agency or as known to the applicant, of each patent alleged to be invalid or not infringed.

(6) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed. The applicant shall include in the detailed statement:

(i) For each claim of a patent alleged not to be infringed, an explanation of why the claim is not infringed.

(ii) For each claim of a patent alleged to be invalid, an explanation of the grounds supporting the allegation, including all statutory bases, affirmative defenses, reasoning, and evidence supporting the allegation, citing any relevant case precedent upon which the allegation is based, providing a copy of any patent or publication which is alleged to invalidate such claim and the reasons supporting such allegation.

(iii) For formulation or composition patents, a description of a mechanism through which the applicant agrees to make the formulation or composition of the proposed drug product known to the patent owner or to a designated intermediary who will act as a referee.

(7) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.

(d) *Amendment to an application.* If an application is amended to include the certification described in § 314.50(i), the applicant shall send the notice required by paragraph (a) of this section at the same time that the amendment to the application is submitted to FDA.

(e) *Documentation of receipt of notice.* The applicant shall amend its application to document receipt of the notice required under paragraph (a) of this section by each person provided the notice. The applicant shall include a copy of the return receipt or other similar evidence of the date the notification was received. FDA will accept as adequate documentation of the date of receipt a return receipt or a letter acknowledging receipt by the person provided the notice. An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance. A copy of the notice itself need not be submitted to the agency.

(f) If the above requirements are met, the agency will presume the notice to be complete and sufficient, and it will count the day following the date of receipt of the notice by the patent owner or its representative or by the approved application holder if the holder is an exclusive patent licensee as the first day

of the 45-day period provided for in section 505(c)(3)(C) of the act.

§ 314.53 Submission of patent information.

(a) *Who must submit patent information.* This section applies to any applicant who submits to FDA a new drug application or an amendment to it under section 505(b) of the act and § 314.50 or a supplement to an approved application under § 314.70, except as provided in paragraph (d)(2) of this section.

(b) *Patents for which information must be submitted.* An applicant described in paragraph (a) of this section shall submit information on each patent that claims the drug or a method of using the drug that is the subject of the new drug application or amendment or supplement to it and with respect 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. For purposes of this part, such patents consist of drug (ingredient) patents, drug product (formulation and composition) patents, and method of use patents. Process patents are not covered by this section and information on process patents may not be submitted to FDA. For patents that claim a drug or drug product, the applicant shall submit information only on those patents that claim an approved drug product or a drug product for which the applicant has submitted an application to obtain FDA approval. For patents that claim a method of use, the applicant shall submit information only on those patents that claim approved indications or other conditions of use or that claim indications or other conditions of use for which the applicant is seeking approval in an application.

(c) *Reporting requirements.* (1) *General requirements.* An applicant described in paragraph (a) of this section shall submit the following information for each patent described in paragraph (b) of this section:

(i) Patent number and the date on which the patent will expire.

(ii) Type of patent, i.e., drug, drug product, or method of use.

(iii) Name of the patent owner.

(iv) If the patent owner or applicant does not reside or have a place of business within the United States, the name of an agent (representative) of the patent owner or applicant who resides or maintains a place of business within the United States authorized to receive notice of patent certification under sections 505(b)(3) and 505(j)(2)(B) of the act and §§ 314.52 and 314.95.

(2) *Formulation or composition patents.* (i) *Original certification.* For each formulation or composition patent, in addition to the patent information described in paragraph (c)(1) of this section the applicant shall submit the following certification:

The undersigned certifies that the drug and the formulation or composition of *(name of drug product)* is claimed by Patent No. _____. This product is *(currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act) [or] (the subject of this application for which approval is being sought).*

(ii) *Amendment of patent information upon approval.* Within 30 days after the date of approval of its application, if the application contained a certification required under paragraph (c)(2)(i) of this section, the applicant shall by letter amend the certification to identify each patent that claims the formulation and composition that has been approved.

(3) *Method of use patents.*—(i) *Original certification.* For a patent that claims a method of using the drug product, the patent information described in paragraph (c)(1) of this section shall be accompanied by the following certification that identifies each relevant patent that claims indications or other conditions of use that are approved or are the subject of the application for which approval is being sought:

The undersigned certifies that Patent No. _____ covers the use of *(name of drug product)* that is *(approved) [or] (the subject of this application for which approval is being sought):*

_____

(ii) *Amendment of patent information upon approval.* Within 30 days after the date of approval of its application, if the application contained a certification required under paragraph (c)(3)(i) of this section, the applicant shall by letter amend the certification to identify the specific indications or other conditions of use that have been approved and each patent that claims the approved indications or other conditions of use.

(4) *No relevant patents.* If the applicant believes that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect 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, it shall so certify.

(5) *Authorized signature.* The certifications required by this section shall be signed by the applicant or patent owner, or the applicant's or patent owner's attorney, agent (representative), or other authorized official.

(d) *When and where to submit patent information.*—(1) *Original application.* An applicant shall submit with its original application submitted under this part, including an application described in section 505(b)(2) of the act, the information described in paragraph (c) of this section on each drug (ingredient), drug product (formulation and composition), and method of use patent issued before the application is filed with FDA and for which patent information is required to be submitted under this section. If a patent is issued after the application is filed with FDA but before the application is approved, the applicant shall submit the required patent information in an amendment to the application under § 314.60.

(2) *Supplements.* (i) If a patent is issued for a drug, drug product, or method of use after an application is approved, the applicant shall submit to FDA the required patent information within 30 days of the date of issuance of the patent.

(ii) An applicant shall submit patent information required under paragraph (c) of this section for a patent that claims the product or method of using the product for which approval is sought in any of the following supplements:

(A) To change the formulation;

(B) To add a new indication or other condition of use, including a change in route of administration;

(C) To change the strength;

(D) To make any other patented change.

(iii) If the applicant submits a supplement for one of the changes listed under paragraph (d)(2)(ii) of this section and existing patents for which information has already been submitted to FDA claim the changed product, the applicant shall submit a certification with the supplement identifying the patents that claim the changed product.

(iv) If the applicant submits a supplement for one of the changes listed under paragraph (d)(2)(ii) of this section and no patents, including previously submitted patents, claim the changed product, it shall so certify.

(v) The applicant shall comply with the requirements for amendment of formulation or composition and method of use patent information under paragraphs (c)(2)(ii) and (3)(ii) of this section.

(3) The applicant shall submit two copies of each submission of patent information, an archival copy and a copy for the chemistry, manufacturing and controls section of the review copy, to the Central Document Room, Center

for Drug Evaluation and Research, Food and Drug Administration, Park Bldg. (Rm. 214), 12420 Parklawn Dr., Rockville, MD 20857 The applicant shall submit the patent information by letter separate from, but at the same time as, submission of the supplement.

(4) Patent information shall be considered to be submitted to FDA as of the date the information is received by the Central Document Room.

(5) Each submission of patent information, except information submitted with an original application, and its mailing cover shall bear prominent identification as to its contents, i.e., "Patent Information, or, if submitted after approval of an application, "Time Sensitive Patent Information.

(e) *Public disclosure of patent information.* FDA will publish in the list the patent number and expiration date of each patent that is required to be, and is, submitted to FDA by an applicant, and for each use patent, the approved indications or other conditions of use covered by a patent and any unapproved indications or condition of use to which the applicant certified. FDA will publish such patent information upon approval of the application, or, if the patent information is submitted by the applicant after approval of an application as provided under paragraph (d)(2) of this section, as soon as possible after the submission to the agency of the patent information. Patent information submitted by the last working day of a month will be published in that month's supplement to the list. Patent information received by the agency between monthly publication of supplements to the list will be placed on public display in FDA's Freedom of Information Staff. A request for copies of the file shall be sent in writing to the Freedom of Information Staff (HFI-35), Food and Drug Administration, Rm. 12A-16, 5600 Fishers Lane, Rockville, MD 20857

(f) *Correction of patent information errors.* If any person disputes the accuracy or relevance of patent information submitted to the agency under this section and published by FDA in the list, or believes that an applicant has failed to submit required patent information, that person must first notify the agency in writing stating the grounds for the disagreement. Such notification should be directed to the Office of Drug Standards (HFD-200), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. The agency will then request of the applicable new drug application holder that the correctness of the patent information or omission of patent information be confirmed. Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list. If the new drug application holder does not change the patent information submitted to FDA, a 505(b)(2) application or an abbreviated new drug application under section 505(j) of the act submitted for a drug that is claimed by a patent for which information has been submitted must, despite any disagreement as to the correctness of the patent information, contain an appropriate certification for each listed patent.

§ 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 change may, except as provided in paragraph (b), 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 (3), (e), and (g).

(ii) The information required under § 314.50(d)(2), (4) (if an anti-infective drug), (5), and (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 § 314.53 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 § 314.50(i) 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.

(vii) If the applicant believes the change for which it is seeking approval is entitled to a period of exclusivity, the information required under § 314.50(j).

(2) The applicant shall submit a review copy that contains the technical sections described in § 314.50(d)(1) and (3), and the technical sections described in § 314.50(d)(2), (4), (5), and (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), (4) (if an anti-infective drug), (5), (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 the extent to which its active ingredient(s) is absorbed or is otherwise made available to the site of action is less than that of the reference listed drug.

§ 314.55 [Removed]

11. Section 314.55 *Abbreviated application* is removed.

§ 314.56 [Removed]

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

12a. 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 under § 314.108(b)(2) 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) 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 under § 314.108(b)(2).

13. Section 314.70 is amended by adding new paragraphs (e) and (f) to read as follows:

§ 314.70 Supplements and other changes to an approved application.

(e) *Claimed exclusivity.* If an applicant claims exclusivity under § 314.108 upon approval of a supplemental application for a change to its previously approved drug product, the applicant shall include with its supplemental application the information required under § 314.50(j).

(f) *Patent information.* The applicant shall comply with the patent information requirements under § 314.53(d)(2).

14. 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.

15. Section 314.80 is amended by removing the word "significant" under 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 under § 314.107 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.

16. Section 314.81 is amended in paragraph (a) by removing "505(j)" and replacing it with "505(k)" and 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–315), 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) to report "at the discretion of the registrant when the change occurs."

17 New Subpart C consisting of §§ 314.92 to 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 meet the monograph for an antibiotic drug for which FDA has approved an application.

(3) Drug products for which FDA made a finding that an abbreviated new drug application was suitable and such finding was announced by notice in the **Federal Register**.

(4) 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). 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 of this chapter 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 with one different active ingredient than the combination reference listed drug and the different active ingredient itself is a listed drug. The petitioner shall also include information to show that:

(1) The active ingredients of its 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(p) 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 submitted 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 new 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.

§ 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), (3), (4), and (5). The applicant shall state whether the submission is an abbreviated application under § 314.94 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 approved petition pursuant to § 10.30 of this chapter or § 314.93, the reference listed drug must be the same as the listed drug referred to in the petition. If the abbreviated new drug application is submitted on the basis of an FDA finding published by notice in the **Federal Register** that an abbreviated new drug application is suitable for the product that is the subject of the abbreviated application, and there is no listed drug, the **Federal Register** notice will be considered the listed drug, and the application must contain a reference to the **Federal Register** citation.

(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 pursuant to § 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 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 is an active ingredient of another listed drug or of a drug which 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 pursuant to 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 which shows that the drug product is bioequivalent to the reference listed drug upon which the applicant relies or to the standard identified in an applicable **Federal Register** notice permitting the submission of an abbreviated new drug application for the drug product, or

(ii) If the abbreviated new drug application is submitted pursuant to a petition to vary an active ingredient, approved under § 314.93, 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 will consider a 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 of the same safety and effectiveness.

(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 protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

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

(ii) *Inactive ingredients.* If an applicant seeks approval of a drug product which differs from the reference listed drug in one or more inactive ingredients or composition, the applicant shall identify and characterize these differences and provide information demonstrating that the differences 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 § 314.94(a)(3). 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 of the proposed drug product.

(iv) *Inactive ingredient changes permitted in drug products intended for ophthalmic 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 § 314.94(a)(3). 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.

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

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

(12) *Patent certification*—(i) *Patents claiming drug, drug product, or method of use.* (A) Except as provided in paragraphs (a)(12)(iv) of this section, a certification with respect to each patent issued by the United States Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or that claims a use of such listed drug for which the applicant is seeking approval under section 505(j) of the act and for which information is required to be filed under section 505 (b) and (c) of the act and § 314.53. For each such patent, the applicant shall provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(*1*) That the patent information has not been submitted to FDA. The applicant shall entitle such a certification "Paragraph I Certification;"

(*2*) That the patent has expired. The applicant shall entitle such a certification "Paragraph II Certification;"

(*3*) The date on which the patent will expire. The applicant shall entitle such a certification "Paragraph III Certification;" or

(*4*) That the patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the abbreviated application is submitted. The applicant shall entitle such a certification "Paragraph IV Certification. This certification shall be submitted in the following form:

I (*name of applicant*), certify that Patent No. _____ (*is invalid or will not be infringed by the manufacture, use, or sale of*) (*name of proposed drug product*) for which this application is submitted.

The certification shall be accompanied by a statement that the applicant will comply with the requirements under § 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with the requirements under § 314.95(c) with respect to the content of the notice.

(B) If the abbreviated new drug application refers to a listed drug that is itself a licensed generic product of a patented drug first approved under section 505(b) of the act, the appropriate patent certification under paragraph (a)(12)(i) of this section with respect to each patent that claims the first-approved patented drug or that claims a use for such drug.

(ii) *No relevant patents.* If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (a)(12)(i) of this section, a certification in the following form:

In the opinion and to the best knowledge of (*name of applicant*), there are no patents that claim the listed drug referred to in this application or that claim a use of the listed drug.

(iii) *Method of use patent.* (A) If patent information is submitted under section 505 (b) or (c) of the act and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, a statement explaining that the method of use patent does not claim any of the proposed indications.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication that, according to the patent information submitted under section 505 (b) or (c) of the act and § 314.53 or in the opinion of the applicant, is claimed by a use patent, an applicable certification under paragraph (a)(12)(i) of this section.

(iv) *Method of manufacturing patent.* An applicant is not required to make a certification with respect to any patent that claims only a method of manufacturing the listed drug.

(v) *Licensing agreements.* If the abbreviated new drug application is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, a certification under paragraph (a)(12)(i)(A)(*4*) ("Paragraph IV Certification") as to that patent and a statement that it has been granted a patent license. If the patent owner consents to an immediate effective date upon approval of the abbreviated

application, the abbreviated application shall contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to an immediate effective date.

(vi) *Late submission of patent information.* If a patent on the listed drug is issued and the holder of the approved application for the listed drug does not submit the required information on the patent within 30 days of issuance of the patent, an applicant who submitted an abbreviated new drug application for that drug that contained an appropriate patent certification before the submission of the patent information is not required to submit an amended certification. An applicant whose abbreviated new drug application is submitted after a late submission of patent information, or whose pending abbreviated application was previously submitted but did not contain an appropriate patent certification at the time of the patent submission, shall submit a certification under paragraph (a)(12)(i) or a statement under paragraph (a)(12)(iii) of this section as to that patent.

(vii) *Disputed patent information.* If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under § 314.53(f). Unless the patent information is withdrawn or changed, the applicant shall submit an appropriate certification for each relevant patent.

(viii) *Amended certifications.* A certification submitted under paragraphs (a)(12) (i) through (iii) of this section may be amended at any time before the effective date of the approval of the application. An applicant shall submit an amended certification as an amendment to a pending application or by letter to an approved application. Once an amendment or letter is submitted, the application will no longer be considered to contain the prior certification.

(A) *After finding of infringement.* An applicant who has submitted a certification under paragraph (a)(12)(i)(A)(*4*) of this section and is sued for patent infringement within 45 days of the receipt of notice sent under § 314.95, shall amend the certification if a final judgment in the action against that applicant is entered finding the patent to be infringed. In the amended certification, the applicant shall certify under paragraph (a)(12)(i)(A)(*3*) of this section that the patent will expire on a specific date. Once an amendment or letter for the change has been submitted, the application will no longer be considered to be one containing a certification under paragraph (a)(12)(i)(A)(*4*) of this section.

(B) *After removal of a patent from the list.* If a patent is removed from the list, for any reason other than because the patent has been declared invalid in a lawsuit brought pursuant to a notice under § 314.95, after one or more applicants have submitted certifications under paragraph (a)(12)(i)(A)(*4*) of this section on that patent, any applicant with a pending application or with an approved application with a delayed effective date who has made such a certification shall amend the certification. The applicant shall certify under paragraph (a)(12)(ii) of this section, if applicable, that no patents described in paragraph (a)(12)(i) of this section claim the drug. If other relevant patents claim the drug, the applicant shall instead submit a request to withdraw the certification under paragraph (a)(12)(i)(A)(*4*) of this section. Once an amendment or letter for the change has been submitted, the application will no longer be considered to be one containing a certification under paragraph (a)(12)(i)(A)(*4*) of this section.

(C) *Other amendments.* (*1*) Except as provided in paragraphs (a)(12)(iv) and (viii)(C)(*2*) of this section, an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application the applicant learns that the submitted certification is no longer accurate.

(*2*) An applicant is not required to amend a submitted certification when information on a patent on the listed drug is submitted after the abbreviated application is approved, whether or not the approval of the abbreviated application is effective.

(b) *Drug products subject to the Drug Efficacy Study Implementation (DESI) review.* (1) If the abbreviated new drug application is for a duplicate of a drug product that is subject to FDA's Drug Efficacy Study Implementation (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.

(2) If the abbreviated new drug application is for a duplicate of a drug product that is subject to FDA's DESI review or other DESI-like review and the drug product evaluated in the review is not a listed drug at the time of submission of the abbreviated application, the applicant shall comply with the conditions set forth in the applicable DESI notice or other notice with respect to conditions of use and labeling and with the provisions of paragraph (a) of this section. However, if a drug product has been approved pursuant to a DESI notice and later withdrawn from sale, the applicant shall follow the procedures in § 314.122.

(c) *Abbreviated antibiotic application.* 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), (3), (4), and (5), (b), (d) (1) and (3), (e), and (g). The applicant shall state whether the submission is an abbreviated application under § 314.94 or a supplement to an abbreviated application under § 314.97

(d) *Format of 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) 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 separately-bound sections. One section shall contain the information described under paragraphs (a) (3) through (6), (8), (9), and (12) of this section and 1 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), (7), and (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 (3). Each of the technical sections in the review copy is required to be separately bound 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.

§ 314.95 Notice of certification of invalidity or noninfringement of a patent.

(a) For each patent that claims the listed drug or that claims a use for such listed drug for which the applicant is seeking approval and that the applicant certifies under § 314.94(a)(12) is invalid or will not be infringed, the applicant shall send notice of such certification by registered or certified mail, return receipt requested to each of the following persons:

(1) Each owner of the patent which is the subject of the certification or the representative designated by the owner to receive the notice. The name and address of the patent owner or its representative may be obtained from the United States Patent and Trademark Office; and

(2) The holder of the approved application under section 505(b) of the act for the listed drug that is claimed by the patent and for which the applicant is seeking approval, or, if the application holder does not reside or maintain a place of business within the United States, the application holder's attorney, agent, or other authorized official. The name and address of the application holder or its attorney, agent, or authorized official may be obtained from the Division of Drug Information Resources (HFD–80), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857

(3) This paragraph does not apply to a use patent that claims no uses for which the applicant is seeking approval.

(b) The applicant shall send the notice required by paragraph (a) of this section when it receives from FDA an acknowledgment letter stating that its abbreviated new drug application is sufficiently complete to permit a substantive review. At the same time, the applicant shall amend its abbreviated new drug application to include a statement certifying that the notice has been provided to each person identified under paragraph (a) of this section and that the notice met the content requirements under paragraph (c) of this section.

(c) *Content of a notice.* In the notice, the applicant shall cite section 505(j)(2)(B)(ii) of the act and shall include, but not be limited to, the following information:

(1) A statement that FDA has received an abbreviated new drug application submitted by the applicant containing any required bioavailability or bioequivalence data or information.

(2) The abbreviated application number.

(3) The established name, if any, as defined in section 502(e)(3) of the act, of the proposed drug product.

(4) The active ingredient, strength, and dosage form of the proposed drug product.

(5) The patent number and expiration date, as submitted to the agency or as known to the applicant, of each patent alleged to be invalid or not infringed.

(6) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed. The applicant shall include in the detailed statement:

(i) For each claim of a patent alleged not to be infringed, an explanation of why the claim is not infringed.

(ii) For each claim of a patent alleged to be invalid, an explanation of the grounds supporting the allegation, including all statutory bases, affirmative defenses, reasoning, and evidence supporting the allegation, citing any relevant case precedent upon which the allegation is based, providing a copy of any patent or publication relied upon, and indicating that portion of each such patent or publication which is alleged to invalidate such claim and the reasons supporting such allegation.

(iii) For formulation or composition patents, a description of a mechanism through which the applicant agrees to make the formulation or composition of the proposed drug product known to the patent owner or to a designated intermediary who will act as a referee.

(7) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.

(d) *Amendment to abbreviated application.* If an abbreviated application is amended to include the certification described in § 314.94(a)(12)(i)(A)(*4*), the applicant shall send the notice required by paragraph (a) of this section at the same time that the amendment to the abbreviated application is submitted to FDA.

(e) *Documentation of receipt of notice.* The applicant shall amend its abbreviated application to document receipt of the notice required under paragraph (a) of this section by each person provided the notice. The applicant shall include a copy of the return receipt or other similar evidence of the date the notification was received. FDA will accept as adequate documentation of the date of receipt a return receipt or a letter acknowledging receipt by the person provided the notice. An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance. A copy of the notice itself need not be submitted to the agency.

(f) If the above requirements are met, FDA will presume the notice to be complete and sufficient, and it will count the day following the date of receipt of the notice by the patent owner or its representative or by the approved application holder if the holder is an exclusive patent licensee as the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the act. FDA may, if the applicant amends its ANDA with a written statement that a later date should be used, count from such later date.

§ 314.96 Amendments to an unapproved abbreviated application.

(a) *Abbreviated new drug application.* (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) Ordinarily, an amendment submitted before the end of the 180-day review period will not extend the review period. If, however, the agency concludes that an amendment contains significant new data requiring additional time for agency review, FDA will extend the review period, but only for the length of time needed to review the submission and for no more than 180 days. The agency will notify the applicant of the length of the extension.

(3) Submission of an amendment to resolve substantial deficiencies in the application as set forth in a not approvable letter issued under § 314.120 will extend the review period for 120 days from the date of receipt by FDA of the amendment. The submission of such an amendment constitutes an agreement by 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.

(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.

§ 3 14.98 Postmarketing reports.

(a) Except as provided in paragraphs (b) and (c) 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 under § 314.107 shall comply with the requirements of § 314.80 regarding the reporting of adverse drug experiences.

(b) Except as provided in paragraph (c) of this section, the 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) Periodic reporting of adverse drug experiences under § 314.80(c)(2) is not required if no adverse drug experience reports have been received and no labeling changes have been initiated by the applicant during the reporting interval.

(d) 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.

18. Part 314 is amended by revising the heading for Subpart D, §§ 314.100, 314.101, and 314.102 to read as follows:

Subpart D—FDA Action on Applications and Abbreviated Applications

§ 314.100 Time frames 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, 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.

§ 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 application 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 apply, 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 paragraphs (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 pursuant to § 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 because 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 addresses 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, or, for each study not conducted in compliance with Part 58, 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; 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 abbreviated new drug application contains a certification under § 314.94(a)(12)(i)(A)(*4*), but does not contain the results of any required and completed bioequivalence or bioavailability study, or, if appropriate, a request for waiver of such study requirement.

(e) The agency will refuse to file an application or abbreviated antibiotic application or will consider an abbreviated new drug application not to have been received if any of the following applies:

(1) 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 a repackager of the already approved drug product.

(2) The drug product is subject to licensing by FDA under the Public Health Service Act (58 Stat. 632 as amended (42 U.S.C. 201 *et seq.*)) and Subchapter F of Chapter I of Title 21 of the Code of Federal Regulations.

(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.

§ 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. 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's 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 which have been identified by that time and which 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.

19. 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.

20. Part 314 is amended by revising §§ 314.104 and 314.105 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.

§ 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 send the applicant an approval letter if none of the reasons in § 314.125 for refusing to approve the application or abbreviated antibiotic application apply. The date of the agency's approval letter is the date of approval of the application or abbreviated antibiotic application. 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 letter is issued, except that a new drug product subject to a 505(b)(2) application may not be marketed until approval of the application is effective under § 314.107 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 antibiotic application after it determines that the drug meets the statutory standards for manufacturing and controls, and labeling. 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 apply. The date of the agency's approval letter is the date of approval of the abbreviated new drug application. 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 under § 314.107 Ordinarily, the effective date of approval will be stated in the approval letter.

21. Part 314 is amended by adding §§ 314.107 and 314.108 to read as follows:

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

(a) *General.* A drug product may be introduced or delivered for introduction into interstate commerce when approval of the application or abbreviated application for the drug product becomes effective. Except as provided in this section, approval of an application or abbreviated application for a drug product becomes effective on the date FDA issues an approval letter under § 314.105 for the application or abbreviated application.

(b) *Effect of patent on the listed drug.* If approval of an abbreviated new drug application submitted under section 505(j) of the act or of a 505(b)(2) application is granted, that approval will become effective in accordance with the following:

(1) *Date of approval letter.* Except as provided in paragraph (c) of this section, approval will become effective on the date FDA issues an approval letter under § 314.105 if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that:

(i) There are no relevant patents, or

(ii) The applicant is aware of a relevant patent but the patent information required under section 505 (b) or (c) of the act has not been submitted to FDA, or

(iii) The relevant patent has expired, or

(iv) The relevant patent is invalid or will not be infringed.

(A) The patent owner or its representative or the exclusive patent licensee has not brought suit for patent infringement within 45 days of the receipt of the applicant's notice of certification required under § 314.52 or § 314.95, or

(B) The drug product is covered by a patent licensing agreement and the abbreviated new drug application or 505(b)(2) application includes:

(*1*) A statement that the applicant has been granted a patent license;

(*2*) A statement from the patent owner that it has a licensing agreement with the applicant covering the proposed drug product and consents to an immediate effective date; and

(*3*) The patent owner's name and address.

(2) *Upon patent expiration.* If the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the relevant patent will expire on a specified date, approval will become effective on the specified date.

(3) *Upon disposition of patent litigation.* (i)(A) Except as provided in paragraphs (b)(3) (ii), (iii), and (iv) of this section, if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the relevant patent is invalid or will not be infringed, and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement within 45 days of receipt of the notice of certification from the applicant under § 314.52 or § 314.95, approval will be made effective 30 months after the date of the receipt of the notice of certification by the patent

owner or by the exclusive licensee (or their representatives) unless the court has extended or reduced the period because of a failure of either the plaintiff or defendant to cooperate reasonably in expediting the action, or

(B) If the patented drug product qualifies for 5 years of exclusive marketing under § 314.108(b)(2) and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement during the 1-year period beginning 4 years after the date the patented drug was approved and within 45 days of receipt of the notice of certification, the 30-month period will be extended by an amount of time, if any, that is required for 7½ years to have elapsed from the date of approval of the application for the patented drug product and approval will be made effective at the expiration of the 7½ years.

(ii) If before the expiration of the 30-month period, or 7½ years where applicable, the court issues a final order that the patent is invalid or not infringed, approval will be made effective on the date the court enters judgment,

(iii) If before the expiration of the 30-month period, or 7½ years where applicable, the court issues a final order that the patent has been infringed, approval will be made effective on the date the court determines that the patent will expire or otherwise orders, or

(iv) If before the expiration of the 30-month period, or 7½ years where applicable, the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug product until the court decides the issues of patent validity and infringement, and if the court later decides that the patent is invalid or not infringed, approval will be made effective on the date the court enters final judgment.

(4) *Multiple certifications.* If the applicant has submitted certifications under § 314.50(i) or § 314.94(a)(12) for more than one patent, the date of approval will be calculated for each certification, and the approval will become effective on the last applicable date.

(c) *Subsequent abbreviated new drug application submission.* (1) If an abbreviated new drug application contains a certification that a relevant patent is invalid or will not be infringed and the application is for a generic copy of the same listed drug for which an abbreviated new drug application was previously submitted containing a certification that the same patent was invalid or would not be infringed and the previous applicant has been sued for patent infringement within 45 days of the patent owner's receipt of notice submitted under § 314.95, approval of the subsequent abbreviated new drug application will be made effective no sooner than 180 days from whichever of the following dates is earlier:

(i) The date the first of the previous applicants to submit a substantially complete abbreviated new drug application containing a certification that a patent on the listed drug was invalid or not infringed and to be sued within 45 days of the patent owner's receipt of notice submitted under § 314.95 first commences commercial marketing of its drug product, or

(ii) The date of a decision of the court holding the relevant patent invalid or not infringed.

(2) For purposes of paragraph (c)(1) of this section, an abbreviated new drug application will be considered to have been "previously submitted" with respect to another application for the same listed drug if the date on which the first application was both substantially complete and contained a certification that the patent was invalid or not infringed is earlier than the date on which the second application was both substantially complete and contained the same certification. A "substantially complete" application must contain the results of any required bioequivalence studies, or, if applicable, a request for a waiver of such studies.

(3) For purposes of paragraph (c)(1) of this section, if the "first applicant" described in paragraph (c)(1)(i) of this section has not yet received approval of its abbreviated new drug application, FDA will make the approval of subsequent abbreviated applications immediately effective if FDA concludes that the first applicant is not actively pursuing approval of its abbreviated application.

(4) For purposes of paragraph (c)(1)(i) of this section, the first applicant that makes a certification that one or more patents on a drug is invalid or will not be infringed and that has been sued for patent infringement shall notify FDA of the date that it commences commercial marketing of its drug product. Commercial marketing commences with the first date of introduction or delivery for introduction into interstate commerce outside the control of the manufacturer of a drug product, except for investigational use under 21 CFR Part 312, but does not include transfer of the drug product for reasons other than sale within the control of the manufacturer or application holder. If an applicant does not promptly notify FDA of such date, the effective date of approval shall be deemed to be the date of the commencement of first commercial marketing.

(d) *Delay due to exclusivity.* The agency will also delay the effective date of the approval of an abbreviated new drug application under section 505(j) of the act or a 505(b)(2) application if delay is required by the exclusivity provisions in § 314.108. When the effective date of an application is delayed under both this section and § 314.108, the effective date will be the later of the 2 days specified under this section and § 314.108.

(e)(1) References to actions of "the court" in paragraphs (b) and (c) of this section are to the court that enters final judgment from which no appeal can be or has been taken.

(2) For purposes of establishing the effective date of approval based on a court judgment, the applicant shall submit to the Division of Generic Drugs (HFN-230), within 10 working days of a final judgment, a copy of the entry of judgment.

(f) *Computation of 45-day time clock.* (1) The 45-day clock described in paragraph (b)(3) of this section begins on the day after the date of receipt of the applicant's notice of certification by the patent owner or its representative, or by the approved application holder if the holder is an exclusive patent licensee. When the 45th day falls on Saturday, Sunday, or on a Federal holiday, the 45th day will be the next day that is not a Saturday, Sunday, or a Federal holiday.

(2) If the applicant of the abbreviated new drug application or 505(b)(2) application does not notify FDA in writing before the expiration of the 45-day time period or the completion of the agency's review of the application, whichever occurs later, that a legal action for patent infringement was filed within 45 days of receipt of the notice of certification, approval of the abbreviated new drug application or 505(b)(2) application will be made effective immediately upon expiration of the 45 days or upon completion of the agency's review and approval of the application, whichever is later. The 505(b)(2) applicant or abbreviated new drug applicant shall notify FDA of the filing of any such legal action and shall include in such notification:

(i) The abbreviated new drug application or 505(b)(2) application number.

(ii) The name of the abbreviated new drug application or 505(b)(2) applicant.

(iii) The established name of the drug, if any, strength, and dosage form.

(iv) A certification that action to defend the patent, identified by number, has been filed in an appropriate court on a specified date. The applicant of an abbreviated new drug application shall send the notification to FDA's Division of Generic Drugs (HFD–230). A 505(b)(2) applicant shall send the notification to the appropriate division in the Center for Drug Research and Evaluation reviewing the application.

(3) If the patent owner or approved application holder who is an exclusive patent licensee waives its opportunity to file a legal action for patent infringement within 45 days of receipt of the notice of certification and the patent owner or approved application holder who is an exclusive patent licensee submits to FDA a valid waiver before the 45 days elapses, approval of the abbreviated new drug application or 505(b)(2) application will be made effective upon completion of the agency's review and approval of the application. FDA will only accept a waiver in the following form:

(*Name of patent owner or exclusive patent licensee*) has received notice from (*name of applicant*) under (*section 505(b)(3) or 505(j)(2)(B) of the act*) and does not intend to file an action for patent infringement against (*name of applicant*) concerning the drug (*name of drug*) before (*date on which 45 days elapses*). (*Name of patent owner or exclusive patent licensee*) waives the opportunity provided by (*section 505(c)(3)(C) or 505(j)(4)(B)(iii) of the act*) and does not object if (*name of applicant*)'s (*505(b)(2) or abbreviated new drug application*) for (*name of drug*) is approved with an immediate effective date on or after the date of this letter.

§ 314.108 New drug product exclusivity.

(a) The following definitions of terms apply to this section:

Active moiety" means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

Approved under section 505(b)" means an application submitted under section 505(b) and approved on or after October 10, 1962, or an application that was "deemed approved" under section 107(c)(2) of Pub. L. 87–781.

"Clinical investigation" means any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on human subjects.

"Conducted or sponsored by the applicant" with regard to an investigation means that before or during the investigation, the applicant was named in Form FDA 1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation. Ordinarily, substantial support will mean providing 50 percent or more of the cost of conducting the study. A predecessor in interest is an entity, e.g., a corporation, that the applicant has taken over, merged with, or purchased, or from which the applicant has purchased all rights to the drug. Purchase of a clinical investigation itself or the rights to an investigation after it is completed is not sufficient to satisfy this definition.

"Date of approval" means the date on the letter from the Food and Drug Administration (FDA) stating that the new drug application is approved, whether or not final printed labeling or other materials must yet be submitted as long as approval of such labeling or materials is not expressly required.

"Essential to approval" with regard to an investigation means that the application could not be approved by FDA without that investigation, even with a delayed effective date.

"New chemical entity" means a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act.

"New clinical investigation" means an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product. For purposes of this section, data from a clinical investigation previously submitted for use in the comprehensive evaluation of the safety of a drug product but not to support the effectiveness of the drug product would be considered new.

(b) *Submission of and effective date of approval of an abbreviated new drug application submitted under section 505(j) of the act or a 505(b)(2) application.* (1) If a drug product that contains a new chemical entity was approved between January 1, 1982, and September 24, 1984, in an application submitted under section 505(b) of the act, the agency will not make effective for a period of 10 years from the date of approval of the first approved new drug application the approval of a 505(b)(2) application or an abbreviated new drug application submitted under section 505(j) of the act for a drug product that contains the same active moiety in the new chemical entity in the first approved application.

(2) If a drug product that contains a new chemical entity was approved after September 24, 1984, in an application submitted under section 505(b) of the act, no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application, except that the 505(b)(2) application or abbreviated application may be submitted after 4 years if it contains a certification of patent invalidity or noninfringement described in § 314.50(i)(1)(i)(*a*)(*4*) or § 314.94(a)(12)(i)(A)(*4*).

(3) The approval of a 505(b)(2) application or abbreviated application described in paragraph (b)(2) of this section will become effective as provided in § 314.107(b) (1) or (2), unless the owner of a patent that claims the drug or the patent owner's representative, or exclusive licensee brings suit for patent infringement against the applicant during the 1-year period beginning 48 months after the date of approval of the new drug application for the new chemical entity and within 45 days after receipt of the notice described at § 314.52 or § 314.95, in which case, approval of the 505(b)(2) application or abbreviated application will be made effective as provided in § 314.107(b)(3).

(4) If an application:

(i) Was submitted under section 505(b) of the act;

(ii) Was approved after September 24, 1984;

(iii) Was for a drug product that contains an active moiety that has been previously approved in another application under section 505(b) of the act; and

(iv) Contained reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application, the agency will not make effective for a period of 3 years after the date of approval of the application the approval of: a 505(b)(2) application or an abbreviated new drug application for the conditions of approval of the original application, or an abbreviated new drug application

submitted pursuant to an approved petition under section 505(j)(2)(C) of the act that relies on the information supporting the conditions of approval of an original new drug application.

(5) If a supplemental application:

(i) Was approved after September 24, 1984, and

(ii) Contained reports of new clinical investigations (other than bioavailability studies) that were conducted or sponsored by the applicant that were essential to approval of the supplemental application, the agency will not make effective for a period of 3 years after the date of approval of the supplemental application the approval of a 505(b)(2) application or an abbreviated new drug application for a change, or an abbreviated new drug application submitted pursuant to an approved petition under section 505(j)(2)(C) of the act that relies on the information supporting a change approved in the supplemental new drug application.

22. Part 314 is amended by revising §§ 314.110 and 314.120 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, 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 under § 314.105 or refuse to approve the 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 paragraphs (a) (1), (2), (3), or (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 in the draft labeling are corrected and final printed labeling is submitted. The approvable letter will describe the labeling deficiencies and state a time period within which the applicant must respond. Unless the applicant corrects the deficiencies by amendment or submits final printed labeling within the specified time period, FDA will refuse to approve the abbreviated application under § 314.127

§ 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), 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), 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, 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 section 505(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 505(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 505(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 505(j)(4)(A) of the act, so that the applicant can determine whether to respond further under paragraphs (a) (1), (2), (3), or (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) 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.

23. New § 314.122 is added to Subpart D to read as follows:

§ 314.122 Submitting an 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 the procedures in § 314.161.

(c) An abbreviated new drug application described in paragraph (a) of this section will be disapproved, pursuant to § 314.127(k), and a 505(j)(2)(C) petition described in paragraph (a) of this section will be disapproved, pursuant to § 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.

24. 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), (9), (10), (12), (14), (15), (16), and by adding new paragraph (b)(17) 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.

(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 56 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) For a new drug, the application failed to contain the patent information required by section 505(b)(1) of the act and § 314.53.

24a. New § 314.127 is added to Subpart D to read as follows:

§ 314.127 Refusal to approve an abbreviated new drug application.

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:

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

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

(c)(1) 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.

(2) 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

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

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

(A) That the other active ingredients are the same as the active ingredients of the reference listed drug, or

(B) 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) of the act, or

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

(d)(1) 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

(2) 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.

(e) If the abbreviated new drug application was submitted pursuant to 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;

(f)(1) 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, (2) if the abbreviated new drug application was submitted pursuant to 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;

(g) 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;

(h)(1) Information submitted in the abbreviated new drug application or any other information available to FDA shows that:

(i) The inactive ingredients of the drug product are unsafe for use, as described in paragraph (h)(2) of this section, under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug product, or

(ii) The composition of the drug product is unsafe, as described in paragraph (h)(2) 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;

(2)(i) FDA will consider the inactive ingredients or composition of a drug product unsafe and refuse to approve an abbreviated new drug application under paragraph (h)(1) 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 raise 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 raise serious questions of safety include:

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

(B) 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.

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

(D) 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.

(E) The use of a controlled release mechanism never before approved for the drug.

(F) A change in composition to include a significantly higher concentration of one or more inactive ingredients than previously used in the drug product.

(G) 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.

(ii) 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.

(iii) 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 toxicity 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 toxicity 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.

(i) 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);

(j) Approval of the reference listed drug has been withdrawn under § 314.151 or FDA has proposed to withdraw approval of the reference listed drug under § 314.151(a);

(k) 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);

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

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

25. 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) 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 applies:

(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 is 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.

(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 assure 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.

(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 apply to the drug. FDA will consider a written request for 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.

26. New § 314.151 is added to Subpart D to read as follows:

§ 314.151 Withdrawal of approval of an abbreviated new drug application pursuant to 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 proposes 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 office of the Dockets Management Branch 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.

27 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 pursuant to section 505(j)(6) of the act and shall satisfy the requirement of § 314.162(b).

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

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

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

(1) The Secretary, pursuant to 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, pursuant to the procedures set forth in paragraph (b) of this section, issues a final decision stating his 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 the 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, Rm. 4-62, 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 are 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 pursuant to paragraph (b)(1) of this section and remove from the list the listed drug and any drug whose approval was suspended pursuant to 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.

29. 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** announcing the approval.

30. 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 or 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, pursuant to § 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 pursuant to §§ 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, pursuant to § 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 pursuant to § 314.150(a) or § 314.151 or pursuant to 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 pursuant to § 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 a notice announcing the removal of a drug from the list in the **Federal Register**.

(c) At the end of the period specified in paragraph (a) (1) or (2) of this section, FDA will relist a drug that has been removed from the list. The agency will publish a notice announcing the relisting of the drug in the **Federal Register**.

31. Section 314.200 is amended by revising the introductory text of paragraph (a), paragraphs (b) (1) and (2), the last sentence in paragraph (c)(1), and 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 abbreviated application or to withdraw the approval of an application or abbreviated application pursuant to 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) *Notice of participation and request for a hearing, and submission of studies and comments.* 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.

32. 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 (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. The 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) 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:

33. Section 314.440 is amended by revising the section heading and paragraph (a), introductory text, and paragraphs (a) (1) and (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 Central Document Room, Center for Drug Evaluation and Research, Park Bldg., Rm. 214, 12420 Parklawn Dr., Rockville, MD 20852. Applicants may obtain folders for binding applications from that office. 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, resubmissions, and other correspondence about an abbreviated application should be directed to the Division of Generic Drugs (HFD–230). Applicants may obtain folders for binding abbreviated applications from that office.

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

34. Part 320 is amended by revising the table of contents, by adding an authority citation to follow the table of contents, and by removing the authority citations following § 320.1 and the authority citations following the headings for Subparts B and C to read as follows:

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

Subpart A—General Provisions

Sec.

Subpart B—Procedures for Determining the Bioavailability or Bioequivalence of Drug Products

Authority: Secs. 201(p), 501, 502, 505, 701(a) (21 U.S.C. 321(p), 351, 352, 355, 371(a)).

§ 320.1 [Amended]

35. Section 320.1 is amended by revising paragraphs (a) and (e), and by removing paragraph (f) to read as follows:

329 § 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 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.

36. Part 320 is amended by revising the heading for Subpart B, §§ 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 paragraph (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 applicant 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 in vivo bioavailability or bioequivalence shall meet the criteria set forth in § 320.22.

(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 the Food and Drug Administration (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 is considered self-evident if the product meets one of the following criteria:

(1) The drug product:

(i) Is a solution intended solely for intravenous administration, 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 drug 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 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 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 parenteral drug product that is determined to be effective for at least one indication in a Drug Efficacy Study Implementation notice or that, upon submission of evidence, is shown to be identical in both active and inactive ingredient formulation to that drug as currently approved in a new drug application, if the drug product is not one of the following:

(1) A drug in suspension form.

(2) Phenytoin sodium powder for injection.

(d) 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.

(e) 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 following conditions 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.

(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.

(f) 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.

(g) 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 338 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 its active metabolites, 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 its active metabolites 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 its active metabolites 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 active moiety and its active metabolites 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 (2) of this section, when the approaches described in paragraphs (b)(1) (ii) and (iii) and (b)(3) are not available. This 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) Any other approach deemed adequate to establish bioavailability or bioequivalence by the Food and Drug Administration (FDA).

(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 the Food and Drug Administration (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–250), 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 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 "Investigational New Drug Application.

(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 "Investigational New Drug Application.

§ 320.50 [Removed]

37 Section 320.50 *Purpose* is removed.

§ 320.51 [Removed]

38. Section 320.51 *Procedures for establishing or amending a bioequivalence requirement* is removed.

§ 320.52 [Redesignated as § 320.32]

39. Part 320 is amended by redesignating § 320.52 as § 320.32 in Subpart B, and by revising the section heading and the introductory paragraph to read as follows:

§ 320.32 Criteria and evidence to assess actual or potential bioequivalence problems.

The Commissioner 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]

40. Section 320.53 *Types of bioequivalence requirements* is removed.

§ 320.54 [Removed]

41. Section 320.54 *Contents of a petition to establish a bioequivalence requirement* is removed.

§§ 320.55 and 320.56 [Redesignated as §§ 320.33 and 320.34]

42. Part 320 is amended by redesignating § 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* as §§ 320.33 and 320.34 in Subpart B, respectively.

§ 320.57 [Removed]

43. Section 320.57 *Requirements for the conduct of in vivo bioequivalence testing in humans* is removed.

§ 320.58 [Removed]

44. Section 320.58 *Requirements for marketing a drug product subject to a bioequivalence requirement* is removed.

§ 320.59 [Removed]

45. Section 320.59 *Bioequivalence requirements based on data voluntarily submitted* is removed.

§ 320.60 [Removed]

46. Section 320.60 *Bioequivalence requirements for a drug product subject to an old drug monograph* is removed.

§ 320.61 [Removed]

47 Section 320.61 *Requirements for in vivo testing of a drug product not meeting an in vitro bioequivalence standard* is removed.

§ 320.62 [Redesignated]

48. Part 320 is amended by redesignating § 320.62 *Requirements for maintenance of records of bioequivalance testing* as § 320.35 in Subpart B.

Dated: March 2, 1989.

Frank E. Young,

Commissioner of Food and Drugs.

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