**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.

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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

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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

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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:

i. *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

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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

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