

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 314

[Docket No. 85N-0214]

RIN 0905-AB63

Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing regulations on certain requirements governing the submission, review, and approval of abbreviated new drug applications (ANDAs). Specifically, these new regulations pertain to patent issues, certification and notice of certification of invalidity or noninfringement of a patent by ANDA applicants, effective date of approval of an application under the Federal Food, Drug, and Cosmetic Act (the act), and new drug product exclusivity. These regulations are intended to complete FDA's implementation of Title I of the Drug Price Competition and Patent Term Restoration Act of 1984.

EFFECTIVE DATE: November 2, 1994.

FOR FURTHER INFORMATION CONTACT: Sharon M. Sheehan, Center for Drug Evaluation and Research (HFD-600), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-0340.

SUPPLEMENTARY INFORMATION:

I. Background

On September 24, 1984, the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the 1984 amendments) was enacted. The law consisted of two different titles. Title I authorized the approval of duplicate versions of approved drug products (other than those reviewed and approved under section 507 of the act (21 U.S.C. 357)) under an ANDA procedure. Title II authorized the extension of patent terms for approved new drug products (including antibiotics and biological drug products), some medical devices, food additives, and color additives. Congress intended these provisions to provide a careful balance between promoting competition among brand-name and duplicate or "generic" drugs and encouraging research and innovation.

Title I also amended section 505 of the act (21 U.S.C. 355) by requiring all

New Drug Application (NDA) applicants and holders to provide certain patent information, requiring ANDA applicants to certify as to the status of patents claiming the drug product they intend to copy, providing 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 requirements were not conducted by the applicant or for which the applicant had not obtained a right of reference or use from the person who conducted the investigations, establishing rules for disclosure of safety and effectiveness data submitted as part of an NDA, and providing specific time periods during which an NDA or an ANDA cannot be submitted or approved. The 1984 amendments also required FDA to promulgate new regulations implementing the statute. In the Federal Register of July 10, 1989 (54 FR 28872), FDA published a proposed rule on Title I. In the Federal Register of April 28, 1992 (57 FR 17950), FDA published a final rule on some aspects of Title I, such as ANDA content and format, approval and nonapproval of an application, and suitability petitions. In that final rule, FDA stated that it was still examining issues concerning patents and market exclusivity, and would issue a final rule once it had completed its deliberations. This document now finalizes those provisions.

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

II. Highlights of the Final Rule

A. 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 (referred to as a 505(b)(2) application) before all relevant product and use patents for the listed drug (a drug product listed in an approved drug product list published by the agency) 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 the 505(b)(2) application may not be made effective until the patent owner and the 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 patents that claim the drug (including product and formulation patents) 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 ("Approved Drug Products With Therapeutic Equivalence Evaluations," also known as the "Orange Book") 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 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. Thus, for example, if the patent expired on January 1, 1995, the effective date of approval of the ANDA or 505(b)(2) application would be January 1, 1995. The agency regards drug products with delayed effective dates as having tentative approvals; it does not consider the approval to be final until the effective date and the issuance of a final approval letter (see 57 FR 17950 at 17956). 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 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 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 final rule describes: (1) The requirements for the submission of patent information by an NDA holder or applicant, (2) the patent certification requirements applicable to generic applicants, and (3) the content of a patent certification notice. The final rule also specifies: (1) When and to whom the notice is to be sent, and (2) the effect of each type of patent certification on

application "contains reports of new clinical investigations (other than bioavailability studies) essential to the approval * * * (see section 505(j)(4)(D)(iii) and (j)(4)(D)(iv) of the act). The phrase "essential to the approval" suggests that the clinical investigations that warrant exclusivity must be vital to the application or supplement. As stated in the preamble to the proposed rule, "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" (see 54 FR 28872 at 28900). For example, the agency would not consider studies to support a switch from prescription to over-the-counter (OTC) status to be "essential to approval" if the agency already had sufficient information to conclude that the OTC product would be safe and effective. (In OTC switch situations, FDA encourages applicants to consult FDA to determine whether clinical investigations or any other actions are necessary to permit FDA to approve a switch in a product's status.)

FDA declines to define in the regulation the kinds of supplemental applications that, if supported by clinical investigations, would warrant 3-year exclusivity. Although the preamble to the proposed rule identified certain types of changes in a product that would normally warrant exclusivity (changes in active ingredient, strength, dosage form, route of administration, or conditions of use), the agency did not intend to suggest that other types of changes would not qualify. For example, changes in dosing regimen have resulted in grants of 3-year exclusivity. Changes that would not warrant exclusivity are, as discussed in the preamble to the proposed rule, changes in labeling that involve warnings or other similar risk information that must be included in the labeling of generic competitors. Applicants obtaining approval for such changes in labeling would, in any event, have no valid interest in precluding such information from the labeling of other products. Furthermore, FDA does not consider a study to be "essential to approval" simply because the applicant conducted it and submitted the study for agency review (Ref. 1).

FDA's interpretation is supported by statements that were made during the congressional debates surrounding the 3-year exclusivity provisions. Senator Orrin Hatch described the 3-year exclusivity provisions upon approval of

certain supplemental applications as protecting "some changes in strength, indications, and so forth, which require considerable time and expense in FDA-required clinical testing" (130 Congressional Record S10505, August 10, 1984) (statement of Senator Hatch)). Representative Henry Waxman said 3-year exclusivity was intended to "encourage drugmakers to obtain FDA approval for significant therapeutic uses of previously approved drugs" (130 Congressional Record H9114, (September 6, 1984)). Thus, an applicant is not entitled to 3-year exclusivity merely because it supplements an approved application based in part on a clinical investigation or because it certifies to FDA that the clinical investigation is essential to approval of the application or supplement.

FDA also declines to create a new procedure whereby a party could contact FDA to determine whether exclusivity information is accurate. Interested parties can obtain information on exclusivity decisions through the Freedom of Information Act process (21 CFR part 20). Parties who wish to challenge an exclusivity decision can utilize the citizen petition procedures (21 CFR 10.30).

96. One comment suggested that products whose labeling may not include certain therapeutic indications (due to exclusivity or patent protection) be listed in the Orange Book as not being therapeutically equivalent to the innovator product.

FDA addressed this comment in its response to a citizen petition submitted by the Pharmaceutical Manufacturers Association (PMA). The response stated, in pertinent part:

In drafting the 1984 Amendments, the only mechanism that Congress provided for enforcing the exclusivity accorded a new indication is the requirement that ANDA's and 505(b)(2) applications be given delayed effective approval for the exclusive indication. During the period that ANDA's and 505(b)(2) applications may not be made effective, pioneers thus have the exclusive right to promote and label their products for the exclusive indication. Nothing in the language of the amended statute or its legislative history, however, suggests that Congress intended the granting of exclusivity for a new indication to alter therapeutic equivalence ratings. Moreover, it would be inconsistent with the established standards for making therapeutic equivalence determinations to rate two products as not therapeutically equivalent simply because one is labeled with fewer than all the approved indications.

FDA's standards for therapeutic equivalence determinations * * * have always been based upon scientific considerations relevant to predicting the comparative pharmacological behavior of two

products in or on the human body. There is no scientific basis for concluding that differences in recommended indications are relevant to this prediction. For example, the fact that a particular brand of drug is recommended in a medical journal article for an unlabeled use, does not, from a scientific standpoint, render other brands of the same drug therapeutically or biologically inequivalent. Similarly, the fact that a pioneer drug is labeled with a protected indication does not mean that generic copies of the same drug are not therapeutically equivalent to the pioneer.

In absence of any suggestion in the statute or legislative history that Congress intended FDA to alter the scientific basis of therapeutic equivalence ratings to enforce exclusivity, FDA declines to consider non-scientific criteria, i.e., the existence of exclusive indications, in making therapeutic equivalence decisions.

(Ref. 2)

FDA has not changed this position and, therefore, declines to adopt the comment.

97. Many comments objected to the definition of "active moiety" and the references to active moieties and new chemical entities throughout proposed § 314.108. The comments said the definitions lacked statutory support and were contrary to two court decisions, *Abbott Laboratories v. Young*, 691 F.Supp. 462 (D. D.C. 1988), remanded, 920 F.2d 984 (D.C. Cir. 1990), and *Glaxo Operations UK Ltd. v. Quigg*, 706 F.Supp. 1224 (E.D. Va. 1989), aff'd, 894 F.2d 392 (Fed. Cir. 1990). Two comments added that the definition of "active moiety" was also too restrictive because it excluded chelates, clathrates, and other noncovalent derivatives. The comments, in general, would delete all references to "active moiety" and "new chemical entity" and refer only to "active ingredients." Some comments would also define "active ingredient" as the active ingredient found in the finished dosage form before the drug is administered to the patient.

Subsequent to the close of the comment period, the interpretation of the act urged by the comments and adopted by the district court in *Abbott Laboratories v. Young* (providing 10 years of exclusivity under section 505(j)(4)(D)(i) of the act for products offering the same therapeutic moiety in different active ingredient forms if the salt or ester form was approved subsequent to the pure therapeutic moiety form) was rejected by the United States Court of Appeals for the District of Columbia. Noting that such an interpretation would award exclusivity to both an active moiety and a salt if the application containing the active moiety were submitted first, but would award exclusivity only to the salt if the salt

Thus, FDA interprets "new clinical investigation" as a clinical investigation whose data have not been relied upon by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug for any indication or safety in a new patient population and do not duplicate the results of another investigation relied upon by FDA to demonstrate a previously approved drug's effectiveness or safety in a new patient population. An applicant is not limited to recently conducted clinical investigations; a clinical investigation that provides a "new" basis for drug approval can qualify for exclusivity.

102. Two comments recommended revising the rule to address transfers of new drug exclusivity between an applicant and all predecessors in interest, including licensors, assignors, joint venture partners, or other parties.

New drug exclusivity is not a property right, but is rather a statutory obligation on the agency. This statutory obligation is based on data and information in an approved application. Although an applicant may purchase an application or rights to data and information in an application (i.e., exclusive rights to a new clinical investigation), from which exclusivity would flow, there is no property right to exclusivity itself that can be transferred separately and apart from the application or data upon which exclusivity is based. The agency does, however, permit the submission or approval of an ANDA when the holder of the exclusivity permits FDA to receive or approve the ANDA.

FDA notes that joint venture partners differ from licensees, assignors, etc., because joint venture partners share in developing a drug product. Consequently, FDA suggests that joint venture partners carefully consider how they will seek approval of an application and define their rights and interests in the application to avoid questions regarding applicability of the exclusivity provisions of the act.

As stated above, FDA has revised the definition of the phrase, "conducted or sponsored by the applicant," to construe a party who has purchased exclusive rights to a study to have "conducted or sponsored" the study. This change will enable a party who has acquired exclusive rights to a study to seek exclusivity.

103. Four comments asked FDA to create a mechanism that would determine whether a study was "essential for approval" either before an application would be submitted or before the study began. Proposed § 314.108(a) stated that "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." The proposal, however, did not discuss the procedure by which FDA would determine a study to be "essential to approval."

FDA declines to accept the comments. FDA cannot determine whether a study is essential for approval until the application is approved. Research goals and objectives often change during clinical investigations. For example, the results from a study designed to support a new indication could generate interest in a completely different indication. The product ultimately approved may be a different product from that characterized in the original application. It is also possible that newly available data in the public domain will obviate the need for the study prior to approval. Thus, FDA will decide whether a study is essential for approval at the time of approval.

The agency has, however, amended the definition of "essential to approval" to delete the reference to a delayed effective date. This change is necessary because the agency no longer regards an application with a delayed effective date as being approved. Instead, FDA considers such applications as being tentatively approved (see 57 FR 17950 at 17953).

104. Proposed § 314.108(b)(2) would provide 5 years of exclusivity for a new chemical entity if a drug product containing the new chemical entity was approved after September 24, 1984, in an application submitted under section 505(b) of the act. One comment said FDA should deny 5-year exclusivity to any section "505(b)(2) application for a new chemical entity that relies upon one or more investigations that are essential for approval of the application but which were not conducted or sponsored by the applicant * * *." The comment explained that a 505(b)(2) applicant could assemble literature demonstrating the safety and effectiveness of a drug product marketed before 1962 (when the Federal Food, Drug, and Cosmetic Act was amended to require new drugs to be safe and effective for their intended uses) or 1938 (when the Food and Drugs Act was amended to require new drugs to be safe for the conditions of their intended use) and, under the rule, seek 5 years of new drug exclusivity. The comment said granting exclusivity to such drugs would be inconsistent with statutory intent and the legislative history.

Under the statute, a drug product may qualify for 5 years of exclusivity if its active moiety has not been previously approved in any other application (see

section 505(c)(3)(D)(ii) and (j)(4)(D)(ii) of the act). For some drug products marketed before 1938 or 1962, the active moiety will have been the subject of an approved application (under prior versions of the act or as part of a combination product approved under the act), so the active moiety will be ineligible for 5-year exclusivity.

FDA also notes that the statute provides 5-year exclusivity for applications approved under section 505(b) of the act and that such applications are submitted by persons who wish to introduce or deliver for introduction into interstate commerce "any new drug." (See section 505(a) and (c)(3)(D)(ii).) The term "new drug" is defined in section 201(p) of the act (21 U.S.C. 321(p)). Drug products with active ingredients marketed before 1938 or 1962 may be "new drugs," especially where there has been a change in the product's labeling, composition, or manufacturer.

Products falling within the definition of a "new drug" must be approved under section 505(b) of the act and, as a result, may qualify for 5-year exclusivity under the language of the act and consistent with legislative history.

105. One comment said that FDA should provide 5 years of exclusivity for a single enantiomer of a previously approved racemate. The comment asserted that FDA approval of a racemic drug mixture covers the mixture rather than the enantiomers that compose the mixture.

The agency declines to revise the rule as requested by the comment. As stated in the preamble to the proposed rule, the agency's position is that "a single enantiomer of a previously approved racemate contains a previously approved active moiety and is therefore not considered a new chemical entity" (see 54 FR 28872 at 28898).

106. One comment asked FDA to interpret the phrase "conditions of approval" in proposed § 314.108(b)(4)(iv) narrowly to limit exclusivity to studies conducted by the original applicant. Proposed § 314.108(b)(4) stated that 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 ANDA for the conditions of approval of the original application, or an ANDA 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 NDA. The comment said subsequent applicants who conduct their own studies to obtain approval should not be subject to the original applicant's exclusivity.

FDA believes that the comment misinterprets the scope of exclusivity. As stated in the preamble to the proposed rule and the preamble to this final rule, market exclusivity does 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 NDA submitted under section 505(b)(1) of the act (see 54 FR 28872 at 28896). As discussed earlier, the statute does not require that the original applicant "conduct" the study to obtain exclusivity. FDA interprets the act to allow for exclusivity where the applicant has supported the study by providing more than 50 percent of the funding or by purchasing exclusive rights to the study.

IV. Analysis of Impacts

FDA has examined the impacts of this rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential

economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact on small entities. Title I of Pub. L. 98-417 eliminated unnecessary regulatory barriers for generic drug products and has resulted in generic competition on many important post-1962 drugs. Generic drug sales account for a significant portion of total prescription drug sales, and many of these sales would not have occurred in the absence of Pub. L. 98-417. This competition has saved consumers hundreds of millions of dollars per year, and FDA concludes that this impact is directly attributable to the statute. This rule will not affect the pace or magnitude of this economic impact. The rule simply clarifies and facilitates implementation of the act. Thus, FDA certifies that this rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or

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

VI. Paperwork Reduction Act of 1980

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

Title: Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions.

Description: The information requirements collect information from persons who must obtain FDA approval before marketing new human drug products or generic versions of previously approved drug products. These persons must submit information to FDA in the form of applications, notices, and certifications. FDA will use this information to determine whether patent information for a drug product has been submitted and whether an applicant is seeking market exclusivity for a particular drug product.

Description of Respondents: Businesses.

ESTIMATED ANNUAL REPORTING AND RECORDKEEPING BURDEN

Section	No. of respondents	No. of responses per respondent	Total annual responses	Hours per response	Total hours
314.50(i)	8	1	8	2	16
314.50(j)	50	1	50	2	100
314.52	30	1	30	8	240
314.53	200	1	200	1	200
314.94(a)(12)	215	1	215	2	430
314.95	30	1	30	16	480
314.107	10	1	10	10	10
Total					1,476

There were no comments received on the Paperwork Reduction Act clearance submission or on the burden estimates. The agency has, however, revised the estimate for ANDA's under § 314.94 based on its latest figures for the number of ANDA's received.

VII. References

The following references have been placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Letter dated September 28, 1992, from Jane E. Henney, Deputy Commissioner for Operations, to Alan H. Kaplan and Richard S. Morey, Kleinfeld, Kaplan and Becker (FDA Docket No. 90P-0455).
2. Letter dated December 8, 1987, from John M. Taylor, Associate Commissioner for Regulatory Affairs, to Bruce J. Brennan, Senior Vice President and General Counsel (FDA Docket No. 86P-0235/CP).