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Guidance for Industry

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administra
Rockville MD 20857

To all NDA or ANDA Holders and Applicants

Dear Sir or Madam:

7/29/88

This is the seventh in a series of letters issued by the Food and Drug Administration to keep you informed of developments in the agency's implementation of the Drug Price Competition and Patent Term Restoration Act of 1984 (the 1984 Amendments). On April 28, 1988, the agency issued a letter compiling agency policies and procedures on the so-called **three and five-year exclusivity provisions** of the 1984 Amendments (the sixth letter). In this seventh letter, the agency is providing related guidance on the so-called **"180-day exclusivity"** provision in section 505(j)(4)(B)(iv) of the Federal Food Drug and Cosmetic Act (the Act), which requires the agency to delay the approval of subsequent ANDAs for a drug product when a previous ANDA applicant has challenged a patent on the listed drug product.

The policies and procedures described in this letter do not resolve every question of interpretation presented by the 180-day exclusivity provision; they are simply those policies and procedures that have been developed in response to particular cases before the agency. The agency expects that as future cases arise, additional policies and procedures will be developed to handle issues not addressed in this letter. If any policy or procedure described in this letter is inconsistent with or modifies previous advice, the new policy or procedure contained in this letter supersedes the previous advice.

I How an ANDA Applicant Qualifies for 180-day Exclusivity.

Section 505(j)(4)(B)(iv) grants to certain ANDA applicants who challenge a patent on a listed drug a 180-day period of marketing free from competition from subsequent ANDA applicants who also allege non-infringement or the invalidity of the patent. FDA believes that Congress intended this provision to reward the first generic applicant to successfully litigate the scope or validity of a patent on a listed drug.

A. The ANDA Must Be the First Complete Application Containing a Paragraph IV Certification.

The statute requires FDA to delay the effective date of an ANDA for 180 days from one of two specified dates when the application contains a certification under 505(j)(2)(A)(vii)(IV) (a paragraph IV certification) and "is for a drug for which a previous application has been submitted under [section 505(j)] containing...a certification [described in subclause iv of section 505(j)(2)(A)(vii)]." To be eligible for the 180-day exclusivity, an ANDA must therefore qualify as a "previous application...containing a [paragraph IV] certification."

As FDA interprets this provision, a "previous application" means a previous substantially complete application. Among other things, a substantially complete application must contain the results of any appropriate bioequivalence studies.[1] An appropriate bioequivalence study is one that meets a specific FDA guidance for the drug product at issue or is otherwise reasonable in design and that purports to show that the proposed drug product is bioequivalent to the listed drug product. Even if the study is ultimately determined to be deficient for reasons that should not have been apparent at the time of filing, the study will be considered adequate to form the basis of a substantially complete application. Neither a protocol nor a pilot study, however, will satisfy these requirements.

To facilitate the implementation of the 180-day exclusivity provision, applications containing paragraph IV certifications are not accepted for filing unless they contain the results of any required bioequivalence studies. If the proposed drug product is one for which the submission of a bioequivalence study is not required for approval, e.g., a parenteral product, the application will be accepted for filing and will be considered a complete application if it contains a request for a waiver of a bioequivalence study and otherwise meets the agency's filing requirements.

The date of submission of a previous application for purposes of determining priority for the 180-day exclusivity will be the date that an application contains both a paragraph IV certification and the appropriate bioequivalence studies.

B. The Applicant Must Be Sued For Patent Infringement.

To qualify for the 180-day exclusivity an applicant must, in addition to being the first to submit a complete application containing a paragraph IV certification, also be sued for patent infringement. FDA bases this interpretation on the logic of the statutory dates from which the 180-day delay runs. The date from which the 180 days runs under subclause (II) of 505(j)(4)(B)(iv) expressly requires that the applicant have won a patent infringement lawsuit.

Moreover, Congress' decision to use the date of "first commercial marketing" as the alternative date in subclause (I) serves a rational purpose only where there has been a lawsuit. It is reasonable to select the date of first commercial marketing rather than the effective date of the ANDA only if an ANDA is in effect but the applicant's decision not to market the drug should be

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[1] FDA's interpretation of "previous application" was upheld in Barr Laboratories v. Bowen (D.C.N.J. Nov. 20, 1987).

encouraged because a delay in marketing serves the public interest. Such a situation occurs where, under the terms of section 505(j)(4)(B)(iii) an ANDA becomes effective 30 months after a lawsuit is filed, but the lawsuit is still unresolved. Because it serves the public interest to permit a defendant in a patent infringement action to stay off the market until the patent issues are resolved, subclauses (I) and (II) were drafted so that the reward of exclusivity would not provide an incentive for immediate marketing: the 180 days does not begin until the applicant wins the lawsuit or actually begins marketing, "whichever is earlier." Outside the context of a lawsuit, however, dating the 180 days from the date of first commercial marketing would protect delays in competition without any countervailing public benefit.

C. First Applicant to Qualify for 180-Day Exclusivity Must "Actively Pursue" ANDA Approval.

Because an applicant can meet all the criteria for the 180-day exclusivity before its ANDA is approved, and because subsequent applications may be delayed for 180 days from the first applicant's approval, an applicant entitled to exclusivity could unreasonably delay the marketing of all generic competitors if the applicant failed to actively pursue approval of its ANDA. Accordingly, FDA will delay the effective date of subsequent ANDA's only so long as the first applicant actively pursues approval of its ANDA.

II How FDA Determines the Date from which 180 Days Runs.

A. "First Commercial Marketing"

The agency defines the date of "first commercial marketing" 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. Commercial marketing does not encompass transfer of a drug product within the control of the manufacturer or application holder for reasons other than sale. An applicant entitled to exclusivity under section 505(j)(4)(B)(iv) who begins commercial marketing of the drug product after the effective date of the ANDA but before completion of the action for patent infringement should notify the Division of Generic Drugs, FDA immediately of the date of first commercial marketing. This notice should be filed with the application.

B. "Court Decision" Includes a Consent Decree

Subclause II specifies as one of the two dates from which the 180 days runs "the date of a decision of a court...holding the patent...to be invalid or not infringed." A final adjudication on the merits is not required to trigger the 180-day period. 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, constitutes "a decision of a court" within the meaning of subclause II. Also, FDA believes that a lawsuit that is settled because the ANDA applicant accepts a license from the patent holder under the patent does not entitle that ANDA applicant to the 180-day exclusivity. A settlement of a lawsuit based upon a licensing agreement does not constitute a decision of the court finding the patent invalid or not infringed because, among other reasons, a license is not necessary for a non-infringing product.

C. Appeal of a District Court Decision

For purposes of determining the date from which the 180-day period runs, the decision of a district court finding a patent invalid or not infringed will be considered the date of a final judgment. The 180 days will begin to run from the date of the initial court's decision even if that decision is appealed, unless the initial court's decision is stayed. (See **Request for Comments** below.)

III Which Subsequent ANDAs Are Delayed?

When an applicant satisfies the criteria for the 180-day exclusivity, FDA will delay until the expiration of the first applicant's exclusivity the effective date of any application that 1) contains a paragraph IV certification, 2) is subsequently submitted, and 3) refers to the same listed drug.

A. "Subsequently Submitted"

As noted above, for purposes of section 505(j)(4)(B)(iv), the date of submission is the date that a substantially completed ANDA is submitted containing, among other things, a paragraph IV certification and any required bioequivalence studies. For example, if applicant "A" submits an ANDA meeting all the agency's filing requirements with a paragraph IV certification on January 1 and then submits a required bioequivalence study on February 1, while applicant "B" submits an ANDA meeting all the agency's filing requirements on January 15, a paragraph IV certification on January 16 and a required bioequivalence study on January 17, ANDA "A" will be considered to have been submitted on February 1, while ANDA "B" will have been submitted on January 17. Thus, ANDA "A" will have been submitted subsequent to ANDA "B" for purposes of potential 180-day exclusivity.

B. Formulation Patents

It has been suggested that section 505(j)(4)(B)(iv) should be applied differently to formulation or composition patents than to active ingredient (substance) patents. Some have argued that, for formulation patents, the exclusivity granted under section 505(j)(4)(B)(iv) should delay the effective date only of subsequent

drug products that raise claims of noninfringement identical or similar to those raised by the applicant entitled to the exclusivity. The basis for this argument is that the 180-day exclusivity is intended as a reward to the first applicant who resolves an issue of the validity or scope of a patent common to subsequent applicants. FDA, does not, however, possess the expertise in patent law to determine whether two formulations raise common patent infringement issues. Moreover, section 505(j)(4)(B)(iv) may be interpreted as providing a reward to the applicant who benefits the public by challenging a patent and allowing competition, even if subsequent generic applicants are not directly benefitted. Because the statutory language permits several interpretations, FDA has concluded that an applicant who obtains exclusivity by challenging a formulation patent delays all subsequent applications that refer to the same listed drug (and contain a paragraph IV certification), even if the products that are the subjects of the subsequent applications have different formulations from the product entitled to exclusivity.

C. Effect of Removal of a Patent from the Orange Book

If a patent is removed from the Orange Book for reasons other than a court decision finding that the patent is invalid after one or more applicants have made paragraph IV certifications, any applicant with a pending application or delayed effective date should submit a new patent certification under section 505(j)(2)(A)(vii)(I) (a "paragraph I certification"). Once a new certification has been submitted, the application will no longer be considered to be an application containing a paragraph IV certification.

IV Request for Comments

When Should the 180-Day Exclusivity Period Begin to Run?

As stated above (at page four) the agency's current policy is that the 180-day exclusivity period begins to run from the date of the initial or district court decision. It has been suggested, however, that a prudent ANDA applicant who is successful in its litigation in the lower court may desire to remain off the market until either the time for appeal of the lower court decision has passed or if an appeal has been taken until the appeal has been decided. Those suggesting this change have said that even with a lower court decision in its favor an ANDA holder may still be liable for treble damages if it loses on appeal. Therefore, they argue that fairness requires that the 180-day exclusivity period should be stayed if the ANDA holder chooses to remain off the market during this time so that the holder is not forced to choose between losing some of its exclusivity or risking potential treble damages.

The agency is interested specifically in comments about whether its current interpretation (that the 180-day exclusivity period begins to run when the initial court decision has been made) should be modified as has been suggested above. Any comment in favor of such changes should include the rationale and policy reasons to support those changes. And, as with all previous letters, I encourage your comments on any of the other policies and interpretations contained in this letter. Comments concerning this letter may be sent to the attention of **Mr. Edwin V. Dutra, Jr., Office of Drug Standards, Center for Drug Evaluation and Research (HFD-203), Room 13-B-22, Parklawn Building, Rockville, Maryland 20857.**

Sincerely yours,

Carl C. Peck, M.D.
Director
Center for Drug Evaluation and Research