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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 Administration
Rockville MD 20857

APR 28 1988

To all NDA or ANDA Holders and Applicants

Dear Sir or Madam:

This is the sixth in a series of letters intended to provide informal notice to all affected parties of developments in policy and interpretation of the Drug Price Competition and Patent Term Restoration Act of 1984. This letter focuses on the so-called three and five-year exclusivity provisions of sections 505(c)(3)(D) and 505(j)(4)(D) of the Federal Food, Drug and Cosmetic Act (the Act), which are available only to drug products for which applications or supplements have been submitted and approved under sections 505 (b) and (c) of the Act. It is also written in response to the numerous requests and inquiries from applicants about how they can assist the Agency in making its exclusivity determinations.

The information below concerning the three-year period of market exclusivity was also discussed in the fourth letter in this series, dated October 31, 1986. To the extent that any information in this sixth letter modifies advice in any previous letter, this information in the sixth letter supercedes the previous advice.

REQUEST FOR EXCLUSIVITY

The Act prohibits the Agency from approving or accepting submission of certain new drug applications if specified criteria are met by other new drug application holders. Thus, the Act does not expressly require that an application holder or applicant apply for or request exclusivity. The prudent applicant or application holder who believes it is entitled to some period of exclusivity, however, may wish to assist the Agency in making its determinations as to whether the criteria are met for exclusivity.

It has been the Agency's experience that most exclusivity determinations cannot be adequately made without information and assistance from the sponsor. This assistance is most efficiently provided where the sponsor includes in its application the data and information necessary to show that it qualifies for exclusivity and indicates where this data and information can be found in the application. Many applicants and holders of applications are already providing this information to the Agency, most commonly as a "request for exclusivity".

The following material is, therefore, intended to provide sponsors with: a concise summary of the criteria contained in the three-year and five-year exclusivity provisions of the Act; a description of the types of data and information the Agency uses to make its determination about exclusivity; and some guidance on how the sponsor can most efficiently call this information to the attention to the Agency staff who must review it. Finally, it must be pointed out that exclusivity determinations are not, and cannot in most instances, be made by the Agency until near the time of approval of an application or supplement. The Agency will make every effort to inform applicants about their exclusivity determinations in the approval letter for the product. In most cases, however, sponsors will learn of the Agency's exclusivity determinations by reviewing the first "Orange Book" supplement that is published after it receives its approval letter.

A. Five-Year Exclusivity
21 U.S.C. 355(j)(4)(D)(ii) and 355(c)(3)(D)(ii)

The five-year period of exclusivity is available only to new chemical entities. The Agency considers a drug product eligible for the five-year period if it contains no active moiety* that was previously approved by the Agency. To assist the Agency in determining which applications meet the criteria for five years of exclusivity, applicants are encouraged to provide the following information when requesting five years of exclusivity.

1. Whether any active moiety in the drug product for which approval is sought has ever been approved in another drug product in the United States either as a single entity or as part of a combination product.

2. If not, whether any active moiety of the drug product has been previously marketed in the United States, and under what name.

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* The "active moiety" in a drug product is the molecule or ion, excluding esterified forms, salts, complexes, chelates, or clathrates 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 five 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 non-covalent derivative (such as a complex, chelate or clathrate) has not been previously approved. A compound (other than an ester) that requires metabolic conversion to produce an already approved active moiety, however, is considered a "new chemical entity" entitled to five years of exclusivity.

B. Three-Year Exclusivity
21 U.S.C. 355(j)(4)(D)(iii),(iv) and 355(c)(3)(D)(iii),(iv)

The three-year period is available to drug products for which the application or supplement to the application contained new clinical investigations (other than bioavailability studies) that were conducted or sponsored by the applicant and were essential to the approval. To assist the Agency in determining which applications meet the three criteria for three years of exclusivity, applicants are encouraged to provide the following information when requesting three years of exclusivity.

1. Whether a drug product containing all the same active ingredients with the same conditions of approval has been previously approved.

2. For purposes of exclusivity determinations, the Agency interprets the phrase "new clinical investigations" to mean investigations conducted on humans that have not been used by the Agency as part of the basis for a finding of substantial evidence of effectiveness for any previously approved new drug application or supplement.

a. Whether, other than a bioavailability or a bioequivalence study, one or more new clinical investigations were submitted to support the application or supplement. (The application should include a certification that to the best of the applicant's knowledge, any such investigation has not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application or supplement.)

b. If the applicant believes that new clinical investigations were submitted, the applicant should specify the volume number(s) and page number(s) of the application where these studies can be found.

3. The Agency interprets the phrase "essential to approval" to mean that the application or supplement could not be approved without the investigation. If an abbreviated new drug application or new drug application described by section 505(b)(2) of the Act or supplement to either could have been approved for the drug product without the submitted studies, even with a delayed effective date, or if publicly available studies, other than those conducted or sponsored by the applicant, could have supported the application or supplement, then the investigation cannot be considered essential to the approval.

To assist the Agency in determining whether the clinical investigation(s) is (are) essential to the approval, the application should include:

a. A list of all published studies and publicly available reports of clinical investigations known to the applicant that are relevant to supporting the conditions of approval sought in the application or the change sought in the supplement.

b. A certification that the applicant has thoroughly searched the scientific literature and that the list of published studies and publicly available reports provided is complete and accurate.

c. A certification that, in the applicant's opinion, there are not sufficient published studies or publicly available reports of clinical investigations (other than those conducted or sponsored by the applicant) to support the approval of the application or the supplement.

4. The Agency considers an investigation to have been conducted or sponsored by the applicant if, before or during the investigation, (1) the applicant was the sponsor named in the Form FDA 1571 (IND) for the investigation, or (2) the applicant, or another entity the applicant purchased or merged with, provided substantial financial support for the investigation.

a. For each clinical study described above that was submitted by the applicant and which the applicant believes is essential to approval of the application, the applicant should state whether it was the sponsor named in the IND or INDs. The IND number of any such study should be identified.

b. If the applicant was not the named sponsor of the INDs, the applicant should state whether it provided substantial support for any of the essential studies. The Agency will attempt to determine whether an applicant's support was substantial from information provided in the application, e.g., whether the applicant provided at least 50% of the cost of conducting any of the studies identified as essential or, if not, a brief explanation as to why the applicant believes its support was substantial.

c. Comments

As with all previous letters, I encourage your comments on these policies and interpretations. 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