

selecting patient representatives, and (2) a plan for soliciting nominations.

A. Qualifications for Patient Representatives

The agency has decided that patient representatives on FDA advisory committees that review and consider cancer therapies will be voting members. Patient representatives will be subject to the same conflict of interest requirements as other committee members as set out in § 14.80 (21 CFR 14.80) and must serve as special Government employees. Section 14.80 defines the qualifications for voting members of advisory committees. FDA recognizes that in some cases the composition of an advisory committee is mandated by statute or regulation. The agency will make a determination to add a voting patient representative on a case-by-case basis when: (1) Meetings are planned; (2) FDA determines it is allowable within the statutes and regulations; and (3) it is feasible and beneficial to a committee's deliberation.

The primary role of the patient representative would be to provide to the advisory committee the perspective of the patients with the disease for which the therapeutic agent is being considered. Currently, many of the FDA advisory committees, including those that provide advice on cancer-related issues, include a representative who is broadly identified with consumer interests and who has been nominated and recommended by a consumer-oriented organization. However, because there are so many different cancers, the number of appropriate perspectives is larger than a single consumer can represent. To more specifically represent the interests of the patients, the FDA believes that a patient representative who understands issues specific to the cancer for which a drug, device, or biologic approval is being sought would bring valuable insights to the FDA advisory committee process. Multiple factors are important to determine the ability of a person to be an effective patient representative. In addition to the qualifications described under § 14.80, the following qualifications are under consideration for selecting patient representatives: (1) Personal experience with an illness, condition, or treatment; (2) experience as a patient advocate; (3) formal affiliation with a patient advocacy organization; (4) ability to articulate the perspective of the patient; (5) ability to identify issues through communications with patient constituencies; (6) ability to access mechanisms to disseminate information from an advisory committee meeting to the affected community; and

(7) experience in technical issues before the committee.

B. Soliciting Nominations

The agency believes that a mechanism for soliciting nominations of qualified patient representatives to ensure broad representation in the nominee pool is critical. After the qualifications for voting patient representatives are defined, the agency proposes to solicit nominations by the following methods: (1) Federal Register announcement as set out in 21 CFR 14.82; and possibly through Internet announcements; (2) direct mailings of announcements and personalized letters to patient advocacy groups, community organizations, and other public interest organizations; (3) patient newsletter announcements; or (4) display announcements at conferences, advisory committee meetings, workshops, etc. that FDA staff members attend, and at other conferences, meetings, and workshops.

Nominations may be submitted by individuals, patient advocacy groups and organizations. Self nominations will also be acceptable.

III. Comments

FDA is seeking the views of the public with regard to the proposed qualifications that should be considered in selecting a patient representative and comments on the adequacy of the methods proposed to obtain nominations. The agency will review and consider written comments on the approach set forth in this notice. Any comments received will be considered in determining whether amendments to, or revisions of, the approach are warranted. Two copies of any comments should be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in the brackets in the heading of this document. Comments received are available for public examination in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Dated: December 30, 1996.

Michael A. Friedman,

Deputy Commissioner for Operations.

[FR Doc. 97-945 Filed 1-14-97; 8:45 am]

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[Docket No. 97N-0002]

Policy on Period of Marketing Exclusivity for Newly Approved Drug Products With Enantiomer Active Ingredients; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is reevaluating its policy on the appropriate period of marketing exclusivity for newly approved drug products whose active ingredient is a single enantiomer of a previously approved racemate. This action is being taken to assess incentives for the development of new enantiomer drug products that may represent significant pharmaceutical advances. The agency is requesting comments on this issue and intends to publish a notice in Federal Register at a later date announcing its policy.

DATES: Written comments by March 17, 1997.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Wayne H. Mitchell, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1049.

SUPPLEMENTARY INFORMATION: FDA is requesting comments on the agency's policy on marketing exclusivity for drug products whose active ingredient is a single enantiomer of a previously approved racemate.

I. Enantiomers and Racemates

Stereoisomers are molecules that have the same constitution (i.e., molecular formula and chemical connectivity), but differ in the spatial orientation of the atoms. When two stereoisomers are mirror images, but are not superimposable upon each other (like left and right hands), they are referred to as enantiomers. Enantiomeric molecules are identical in all physical and chemical properties, except in an environment which is also chiral (characterized by handedness). Polarized light is such an environment, and pairs of enantiomers rotate the plane of polarization by equal amounts in opposite directions. Enantiomers may be either right-handed (dextro-rotary) S(+)-isomers or left-handed (levo-rotary) R(-)-isomers. Racemates are equimolar mixtures of enantiomers of the same molecule.

Frequently, both enantiomers found in a racemate will have similar desirable pharmacological activity. In other cases, one member of a pair of enantiomers is pharmacologically active and the other inactive or nearly inactive, as in baclofen where the R(-)-isomer is a muscle relaxant and antispastic, and the S(+)-isomer is essentially inactive. In other racemates, the enantiomers show significantly different pharmacological activity. For example, both isomers of sotalol have similar antiarrhythmic effects, but only the R(-)-isomer has significant beta-blocking activity. There are also instances where only one member of a pair of enantiomers has shown significant toxicity; an example of this may be found with thalidomide, where it is generally believed that most, if not all, of the teratogenicity associated with the drug is attributable to the R(-)-isomer.

In the past, the usual practice in the pharmaceutical industry has been to develop either a racemate or an enantiomer without fully characterizing or studying its respective properties. When separation of enantiomers was difficult, the question of which stereoisomeric form should be developed was largely an academic question. However, in many cases, current technology permits production of pure enantiomers on a commercial scale. Improved pharmacologic study of enantiomers has been permitted by developments in analytical technology that frequently enable detection of one enantiomer in the presence of the other at concentrations found in biological fluids.

The increased feasibility of such efforts led the agency to issue on May 1, 1992, "FDA's Policy Statement on the Development of New Stereoisomeric Drugs" (Stereoisomeric Drug Policy). (See the Federal Register of May 27, 1992 (57 FR 22249).) The Stereoisomeric Drug Policy provides general recommendations for conducting and reviewing studies of the safety and effectiveness of drug products whose active ingredient is an enantiomer, a racemate, or a nonracemic mixture of enantiomers. Although the Stereoisomeric Drug Policy does not address issues of marketing exclusivity, it does contain the agency's thinking on the approval of stereoisomeric drug products. As such, it may be of interest to anyone commenting on marketing exclusivity for drug products whose active ingredient is a single enantiomer of an approved racemate.

II. Marketing Exclusivity

A. The 1984 Amendments

The 1984 amendments amended the Federal Food, Drug, and Cosmetic Act (the act) to establish two new types of marketing applications: Abbreviated new drug applications (ANDA's), established under section 505(j) of the act (21 U.S.C. 355(j)); and 505(b)(2) applications, established under section 505(b)(2) of the act. The 1984 amendments also provide for the granting of nonpatent marketing exclusivity to certain drug products. Marketing exclusivity gives qualified drug products periods free of competition from drugs approved under ANDA's and 505(b)(2) applications.

Marketing exclusivity is provided for in section 505(c)(3)(D) of the act, which limits approval of competing 505(b)(2) applications, and section 505(j)(4)(D) of the act, which limits approval of competing ANDA's.

Section 505(c)(3)(D)(ii) and (j)(4)(D)(ii) of the act provides that if an NDA is approved for a drug, no active ingredient of which has been approved in a previous NDA, no 505(b)(2) application or ANDA for a drug product with the same active ingredient as the previously approved NDA drug product may be submitted until 5 years after the date of approval of the first drug product.

Section 505(c)(3)(D)(iii) and (j)(4)(D)(iii) of the act provides 3 years of exclusivity to a drug product that includes a previously approved active ingredient, where the NDA for the drug product contains reports of new clinical investigations (other than bioavailability studies), conducted or sponsored by the applicant, that are essential to the approval of the NDA. (Section 505(c)(3)(D) and (j)(4)(D) of the act has other marketing exclusivity provisions which are not relevant to this notice.)

The text of the amendments and the legislative history accompanying the amendments do not directly address how these provisions of the 1984 amendments regarding marketing exclusivity should be applied to enantiomers.

B. Regulations

FDA's regulations implementing the marketing exclusivity provisions of the 1984 amendments are found in § 314.108 (21 CFR 314.108). Section 314.108(b)(2) states that if a drug product that contains a "new chemical entity" was approved in an NDA, "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." Section 314.108(b)(4) states that if an NDA is for a drug product that contains an active moiety that has been previously approved in another NDA, and includes reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the NDA, that drug product will be entitled to 3 years of marketing exclusivity.

"New chemical entity" is defined in § 314.108(a) as "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." "Active moiety" is defined in the same section as follows:

[T]he 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.

The issue of marketing exclusivity for enantiomers is not addressed in the body of the regulation.

In the Federal Register of July 10, 1989 (54 FR 28872), FDA proposed regulations implementing the 1984 amendments. In the preamble to the proposed rule (54 FR 28872 at 28898), FDA briefly examined the issue of whether a single enantiomer of a previously approved racemate is entitled to 5 years of exclusivity under section 505(c)(3)(D)(ii) and (j)(4)(D)(ii) of the act, or 3 years of exclusivity under section 505(c)(3)(D)(iii) and (j)(4)(D)(iii) of the act. The agency stated that:

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.

FDA received one comment disagreeing with the stated policy. This comment was received nearly 4 years after the comment period closed, and the agency responded to it in the preamble to the final rule with a reiteration of the statement from the proposal. (See the Federal Register of October 3, 1994 (59 FR 50338 at 50359).)

III. Request for Comments

In light of the complexity of the scientific and regulatory issues involved, FDA believes it is appropriate to reexamine the question of exclusivity for enantiomers of previously approved

racemates. The agency believes that this issue would benefit from a more focused consideration than it was subject to in the rulemaking process for the regulations implementing the 1984 amendments, where there were many complicated and contentious regulatory matters under consideration, and where this issue was raised by one comment submitted very late in the rulemaking process. Accordingly, FDA is requesting comments on the appropriate period of marketing exclusivity for drug products whose active ingredient is a single enantiomer of a racemate that is an active ingredient of a previously approved drug product. Among the issues that the agency is interested in receiving comment on are as follows:

(1) What period of marketing exclusivity would best effectuate the 1984 amendments' dual policy goals of increasing drug price competition and providing incentives for the development of innovative drug products?

(2) Would granting a 5-year period of exclusivity to enantiomers of previously approved racemates encourage medically significant pharmaceutical innovation?

(3) If the pharmacological action of each enantiomer is described in the approved NDA for the racemate, should a subsequently submitted application for an enantiomer of the racemate receive different treatment for exclusivity purposes than if the pharmacological action of each enantiomer is not described in the approved NDA for the racemate drug product?

(4) If the agency were to assess requests for exclusivity for enantiomers of previously approved racemates on a case-by-case basis, what criteria should the agency apply?

(5) Compared with other drug products, what are the costs of and technical barriers to obtaining safety and efficacy data for a drug product whose active ingredient is a single enantiomer of a previously approved racemate?

(6) How many drug products (whether approved, the subject of pending NDA's, or in development) are likely to be affected by this policy?

After considering comments received in response to this notice, FDA will publish a Federal Register notice setting forth its policy on exclusivity for a drug product whose active ingredient is an enantiomer of a previously approved racemate.

Interested persons may, on or before March 17, 1997, submit to the Dockets Management Branch (address above) written comments regarding this notice.

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. Copies of the comment on exclusivity for enantiomers submitted to the docket for the July 10, 1989, proposed rule; FDA's Stereoisomeric Drug Policy; and other correspondence and documents relating to the subject matter of this notice have been placed in the docket for this notice. Received comments and other material placed in the docket may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Persons considering submitting a 505(b)(2) application or an ANDA for a drug product that may be affected by any change in FDA's policy on marketing exclusivity for enantiomer drug products should contact the Center for Drug Evaluation and Research's (CDER's) Office of Generic Drugs or the appropriate review division within CDER before submitting the application.

Dated: January 10, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97-944 Filed 1-10-97; 12:29 pm]

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Health Resources and Services Administration

Program Announcement for Grant Programs Administered by the Division of Associated, Dental and Public Health Professions, Bureau of Health Professions for Fiscal Year 1997

Correction

In notice document 96-28112 appearing on page 56550 on the issue of Friday, November 1, 1996 make the following correction:

On page 56550, in the table on the fourth line titled "Public Health Special Projects" in the fourth column under the column heading "Available for competing awards", the amount should read "\$2,500,000".

Dated: January 7, 1997.

Ciro V. Sumaya,

Administrator.

[FR Doc. 97-943 Filed 1-14-97; 8:45 am]

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National Institutes of Health

National Cancer Institute; Opportunity for a Cooperative Research and Development Agreement (CRADA) for the Scientific and Commercial Development of Monoclonal Antibodies to a Tumor-Specific Growth Factor for the Diagnosis and Prognosis of Premalignant Lesion and Cancer

AGENCY: National Institutes of Health, DHHS.

ACTION: Notice.

SUMMARY: The National Cancer Institute (NCI) seeks a pharmaceutical or biotechnology company that can effectively pursue the scientific and commercial generation and development of a panel of monoclonal antibodies against an epidermal growth factor (EGF)-related peptide, crypto-1 (CR-1) and its novel receptor. The project is of scientific importance because CR-1 is a protein that exhibits structural homology to the EGF / transforming growth factor α (TGF α) gene family of peptides. As such, CR-1 might function as a growth or survival factor. Therefore, CR-1 may be important as an autocrine or paracrine modulator in such processes as tumor cell growth, wound repair, neovascularization, inflammation, and apoptosis.

NCI has successfully isolated and cloned the gene that encodes CR-1, an EGF-related peptide growth factor that does not bind to the EGF receptor or other type 1 receptor tyrosine kinases. The NCI has also obtained a rabbit anti-peptide polyclonal antibody that can detect the expression of CR-1 in formalin-fixed, paraffin-embedded human tissue sections. CR-1 has been shown to be preferentially and differentially expressed in several different human premalignant lesions and cancers. The selected sponsor will purify a recombinant CR-1 protein and use this material as an immunogen to generate anti-CR-1 monoclonal antibodies for use in the diagnosis and prognosis of human cancers.

ADDRESSES: Inquiries and proposals regarding this opportunity should be sent to Richard I. Kohn, J.D., M.S., Office of Technology Development, National Cancer Institute, as follows: (a) *by U.S. Mail to:* Executive Plaza South, Room 450, 6120 Executive Blvd., MSC 7182, Bethesda MD 20892-7182; (b) *by messengers and express delivery to:* 6120 Executive Blvd, Suite 450, Rockville, MD 20852; (c) *by telephone at* (301) 496-0477; (d) *by fax at* (301) 402-2117.