DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 316

[Docket No. 85N-0483]

RIN 0905-AB55

Orphan Drug Regulations

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing regulations to implement section 2 of the Orphan Drug Act, which consists of four sections added to the Federal Food, Drug, and Cosmetic Act. The Orphan Drug Act directs the agency to provide written recommendations on studies required for approval of a marketing application for an orphan drug. It provides for the designation of drugs, including antibiotics and biological products, as orphan drugs when certain conditions are met, and it provides conditions under which a sponsor of an approved orphan drug enjoys exclusive approval for that drug for the orphan indication for 7 years following the date of the drug's approval for marketing. Finally, section 2 of the Orphan Drug Act encourages sponsors to make orphan drugs available for treatment on an "open protocol" basis before the drug has been approved for general marketing. These proposed regulations specify the procedures for sponsors of orphan drugs to use in availing themselves of the incentives provided for in the Orphan Drug Act and set forth the procedures FDA will use in administering it. These new provisions are intended to benefit consumers by encouraging manufacturers to develop and make available to patients drugs for diseases and conditions that are rare in the United States.

DATES: Comments by April 1, 1991.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, room 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Emery J. Sturniolo, Office of Orphan Products Development (HF-35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4718.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background

In enacting the Orphan Drug Act (Pub. L. 97-414), Congress sought to promote the development of drugs, including antibiotics and biological products, that are needed by, but not available to, people in the United States with "rare diseases or conditions." Congress recognized that the market for drugs intended to treat people with rare diseases or conditions is so limited that the cost of developing the drugs makes a profit by the developer unlikely. Congress concluded that changes in Federal laws were necessary to create incentives for the development of these drugs. Accordingly, Congress enacted the Orphan Drug Act, which included amendments to the Federal Food, Drug, and Cosmetic Act (the act), to create incentives for the development of these drugs by providing, among other incentives, protocol assistance to sponsors of drugs for rare diseases and a 7-year period of exclusive marketing to the holder of the first approval of a designated orphan drug for the orphan indication (21 U.S.C. 360aa-dd).

These proposed regulations, which codify existing administrative practices that implemented the Orphan Drug Act of 1983 and its subsequent amendments (see section II.B. of this preamble), would establish procedures to provide for protocol assistance and to govern exclusive marketing approval. The Orphan Drug Act provides these incentives to assure that drugs that would not otherwise be developed are in fact developed. Thus, these proposed regulations will, where possible, attempt to ensure that the act's incentives are granted only when they would further the purposes of the Orphan Drug Act.

The main purpose of the Orphan Drug Act is to stimulate innovation in developing treatments for patients with rare diseases and conditions and to foster the prompt availability of therapeutically superior drugs. These proposed regulations attempt to ensure that improved therapies will always be marketable, and that orphan drug exclusive approval does not preclude significant improvements in treating rare diseases.

II. Contents of the Program

A. Recommendations for Investigations of Drugs for Rare Diseases or Conditions

Proposed § 316.10 sets forth the procedure for a sponsor to take advantage of section 525 of the act (21 U.S.C. 360aa), which encourages a sponsor of a putative orphan drug to request FDA to provide written recommendations for the nonclinical and clinical investigations required to achieve marketing approval.

Section 525 of the act was intended to reduce the wasted expense and lost time that occur when sponsors carry out investigations under protocols that are unsatisfactory to FDA. This section states that a sponsor may be provided such written recommendations "* * * [if there is] reason to believe that a drug for which a request is made under this section is a drug for a disease or condition which is rare in the States." The provision does not require that a sponsor have actually obtained orphan-drug designation for the subject drug at the time of the request.

FDA has, therefore, determined that, although a review of the sponsor's submission as to whether there is "reason to believe" that the subject drug is an orphan drug would be required for requests for written recommendations, the information and documentation of orphan-drug status to be filed by sponsors with such requests can be less extensive than that required under proposed § 316.20 for designation of an orphan drug under section 526 of the act.

FDA understands that the Orphan Drug Act was enacted to provide incentives, including early agency advice, to sponsors of orphan drugs. The agency believes, however, that it remains the sponsor's responsibility to design and carry out the development of a drug. FDA is neither in a position to design the needed studies *de novo* nor to review the relevant literature or other information on the drug and the disease to be treated to facilitate planning of the development program. So that FDA can provide informed comments on the adequacy of any proposed nonclincial or clinical protocols, the sponsor must include a detailed outline of the proposed study as specified in proposed § 316.10(b) in any request for written recommendations.

FDA intends that any recommendation provided under section 525 of the act and proposed § 316.12 would be the equivalent of an advisory

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opinion under § 10.85 (21 CFR 10.85) of FDA's administrative practices and procedures regulations. The agency would make every effort to adhere to the advice given with respect to the design of studies and the kinds and amounts of data needed for a sponsor's orphan drug to be approved (or licensed) for marketing. FDA may later modify a recommendation if new information becomes available that would place reliance on the recommendation in conflict with good science or the public health. With this exception, however, if a sponsor responsibly follows recommendations related to studies critical to approval, and if the results of the ensuing studies support the safety and effectiveness of the drug, such studies should result in the generation of adequate data to support a marketing application.

Proposed § 316.14 sets forth the reasons why FDA may refuse to provide written recommendations for the nonclinical or clinical investigations required for marketing approval of an orphan drug. The agency expects that most of these reasons will serve as a basis for an agency inquiry to the sponsor seeking more information rather than for an outright refusal to provide such recommendations. However, the sponsor's failure to supply information respecting the results of nonclinical laboratory studies or completed early clinical studies as required by proposed § 316.12(d) or to reply to correspondence respecting the sponsor's request within 90 days as required by proposed § 316.14(c) would lead to a refusal to provide recommendations.

B. Designation of Orphan Drugs

Orphan-drug designation must be obtained before a sponsor can obtain any direct financial benefits that are provided by the Orphan Drug Act. Eligibility for tax credits, for orphan-drug exclusive approval, and for grants and contracts depends upon the sponsor's drug having been designated under section 526 of the act (21 U.S.C. 360bb) as a drug for a specified disease or condition which is rare in the United States. FDA's experience with orphan-drug designations reveals that sponsors have requested designation at all stages in a drug's development, even after FDA's approval of a drug's marketing application. For an interim period after enactment of the Orphan Drug Act on January 4, 1983, FDA provided a grace period during which the agency accepted requests for designation of certain drugs and designated them as orphan drugs after FDA had approved the marketing applications for them. For reasons discussed in a notice published in the **Federal Register** of February 5, 1986 (51 FR 4505), this interim policy was terminated on May 6, 1986. In addition, in Pub. L. 100-290 (the Orphan Drug Amendments of 1988), Congress amended section 526 of the act to require that requests for designation must be made before the submission of a marketing application (see 53 FR 47577; November 23, 1988).

To be designated an orphan drug, a sponsor must show: (1) That the drug is being or will be investigated for a specified rare disease or condition; (2) that the drug would be subject to approval under section 505(b) or 507 of the act (21 U.S.C. 355(b) or 357) or to licensure under section 351 of the Public Health Service Act (42 U.S.C. 262); and (3) that the marketing approval would be for such use or condition.

The 1984 amendments to the Orphan Drug Act (The Health Promotion and Disease Prevention Amendments of 1984) (Pub. L. 98-551) introduced a prevalence figure of 200,000 affected persons as a ceiling for a "rare disease or condition." If a disease or condition affects more than this number, a showing (pursuant to proposed § 316.21) that there is no reasonable expectation that the cost of developing and making available the drug to treat the disease or condition will be recovered from sales in the United States must be made before a drug can be considered an orphan drug.

Congress provided that the 200,000 prevalence figure means 200,000 affected persons in the United States at the time that the orphan-drug designation request is made (not 200,000 new cases annually). Under this proposal, if a drug is designated as an orphan drug because it is intended for a disease or condition with a prevalence of under 200,000, the drug would remain an orphan drug even if the disease or condition ceases to be an orphan disease or condition because of increased prevalence. This approach would protect a sponsor's good-faith investment.

Proposed § 316.29 does provide for discretionary suspension or revocation of orphan-drug designation and, thus, exclusive marketing rights if it is later found that the application for orphan-drug designation: (a) Contained an untrue statement of material fact; or (b) omitted material required information. Also, FDA may suspend orphan-drug designation if it subsequently finds that, as of the date of the submission of the designation request, the drug had in fact not been eligible for designation.

An indication for treatment of a specific disease or condition could involve all patients with that disease or condition or a specified subpopulation of those with the disease or condition. If a drug is under development for only a subset of those persons with a particular disease or condition, orphan-drug designation for use in the limited subset may be granted. Exclusive approval for a disease subset would not bar approval of the same drug for the larger population or other subsets of population by different sponsors, however, if that were later deemed appropriate. In diseases or conditions which are common, subsets would qualify for designation only if the subset is medically plausible. For example, a drug might well be too toxic for use in treating a disease or condition except in patients refractory to or intolerant of other less toxic treatments; the refractory and intolernat patients might be a reaonable orphan subset. On the other hand, choosing an arbitrary subset (e.g., people with blood pressure over a certain level), simply to qualify a drug as an orphan-drug would be unacceptable.

FDA notes that proposed indications for use of orphan drugs are subject to review by the applicable FDA center (e.g., the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research). The centers routinely review indications for use during the approval process. Also, FDA's Office of Orphan Products Development may ask the centers for their advice about the medical plausibility of potential orphan-drug designations. These reviews by the centers include consideration of the appropriateness of the request for orphan-drug designation, and, in particular, consideration of whether the target populations have been artificially restricted.

For most orphan drugs, only one sponsor has requested orphan-drug designation, although in some instances two or more persons each has sought orphan-drug designation for the same drug for the same indication. FDA intends to ensure, however, that a pioneer sponsor's research is not used to give a second sponsor a "free ride." Accordingly, in § 316.20(a), FDA proposes to require that each sponsor's designation request contain all the information needed to allow a determination as to the appropriateness of designation of the product as an orphan-drug even when another sponsor has obtained such designation for the same drug for the same indication is no bar to designation (or, indeed, exclusive approval) of the same drug for a new orphan indication, and § 316.20(a) so provides.

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FDA recognizes that a finding of eligibility for orphan-drug status under the prevalence criteria could apply to all sponsors of drugs for the disease or condition in question. However, FDA believes it unfair to allow a subsequent sponsor to use a pioneer sponsor's research data for the purpose of obtaining orphan-drug designation when such research data would by law not otherwise be available to the subsequent sponsor.

In all cases, the indication for which a drug is designated would have to be the same as, or equivalent to, the ultimately approved indication for exclusive approval to take effect.

FDA understands that the target population for use of a vaccine, diagnostic drug, or preventive drug may be an "at-risk" population that is larger than the population actually affected by the disease or condition. For this reason, proposed §§ 316.20(b)(8) and 316.21(b)(3) would require that sponsors include in any request for designation of such a drug an estimate of the number of people to whom the vaccine, diagnostic drug, or preventive drug will be administered annually in the United States. FDA believes that this provision is justified for such drugs because, even though certain vaccines (e.g., polio vaccine) and other diagnostic/preventive drugs are for rare disorders, they clearly are not orphan drugs because they may be administered to the at-risk target populations of millions of people and thus are not within the class of products contemplated to be covered by orphan-drug legislation.

Under proposed § 316.22, the agency would require foreign sponsors that seek orphan-drug designation to name a permanent-resident agent to whom communications may be made.

Under proposed § 316.26(a), FDA enumerates the reasons for which it would refuse to grant a sponsor's request for orphan-drug designation. In many respects, the reasons why FDA would under § 316.26 deny orphan-drug designation parallel the reasons why FDA may under § 316.14 refuse to provide written recommendations on investigations. As an exception to the general rule, however, proposed § 316.26(b) also provides that FDA may refuse to grant a request for orphan-drug designation if the request contains an untrue statement of material fact. FDA believes that refusal to grant a request in such a circumstance should be discretionary and not mandatory; for example, the untrue statement may be inadvertent.

On the whole, FDA would liberally grant orphan-drug designation when the threshold prevalence or profitability tests are met. FDA would grant orphan-drug designation even for a drug that is otherwise the same drug as one already given exclusive marketing approval under proposal subpart D of part 316 (and during the first drug's period of exclusive approval) when the second sponsor can make a plausible showing that it may be able to produce a clinically superior drug. Approval of such a subsequent drug during the first drug's period of exclusive approval for treatment of the same rare disease or condition would require evidence of the clinical superiority of the subsequent drug, however. The content of this evidence will depend on the nature of the superiority claimed. (See the discussion of the definition of "clinically superior" below.)

FDA considered proposing a rule under which it would designate drugs apparently the same as drugs that already have orphan-drug exclusive approval only where the agency believed that there was a high probability of eventual approval. Such a rule would exclude most drugs that are identical as to active moiety to already approved orphan drugs. FDA decided on a liberal designation policy, however, because the agency wants to encourage research whose aim is to produce safer and more effective drugs, even if FDA believes that the prospects are dim (because of the anticipated difficulty of demonstrating clinical superiority) for eventual marketing approval. FDA believes that a liberal designation policy is appropriate despite the possibility that it might lead to wider use of the tax credit provisions under section 4 of the Orphan Drug Act because the agency doubts that sponsors will deliberately conduct fruitless research just to obtain the tax credits.

Also, the agency is proposing to allow sponsors to apply for amendments to orphan-drug designation up to the time of approval of their marketing applications. The purpose of this proposal is to allow for situations in which testing data unexpectedly demonstrate the effectiveness of drugs in different populations or for different diseases or conditions from that which the drug was initially designated. FDA would grant such an amendment request only if it found that the initial designation request was made in good faith and that the amendment is sought only to render the orphan-drug designation consistent with unanticipated test results. If the prevalence of the disease or condition named in the amendment request exceeds 200,000 people in the United States as of the date of submission of the amendment request, of course, the amendment could not be granted and the drug, when ultimately approved for the new or expanded indication, might be ineligible for exclusive marketing status under the Orphan Drug Act.

FDA is aware that, under Public Law 100–290, no orphan-drug designation request can be granted after the submission of a marketing application. However, FDA does not believe that Congress thereby intended to preclude an amendment to an already existing application for purposes of conforming the designation to the test results.

FDA proposes that this regulation, when final, will apply only prospectively. Therefore, FDA does not plan to reconsider any prior actions under the Orphan Drug Act, or change any orphan-drug status, to conform to the final regulation.

C. Verification of Orphan-Drug Status

An important feature of the definition of an orphan drug is the prevalence figure of 200,000 affected people in the United States as a ceiling for a "rare disease or condition." In accordance with this principle, which was introduced into the Orphan Drug Act by Public Law 98–551 (see section II. B. of this preamble), proposed § 316.21 requires that sponsors of would-be orphan drugs that are designed to treat a condition or disease that affects 200,000 or more persons file detailed statements, including information about marketing costs and justification for revenue projections for the drug. Further, at FDA's request, a sponsor would be required to open its books, including financial records and sales data with respect to the drug proposed for orphan-drug designation, to FDA-appointed auditors. Failure to do so or failure adequately to justify its claims would result in denial of a sponsor's designation request.

FDA recognizes that these data and analysis requirements may be burdensome. FDA believes, however, that the data and information required by proposed § 316.21 to be made available to the agency are necessary to a demonstration of lack of profitability. Allocation of costs is sometimes debatable, and a full disclosure of all cost and profit information related to the drug in question both in the United States and abroad is necessary to satisfy the agency that the sponsor has fulfilled its burden of demonstrating a lack of profitability. However, FDA solicits comments on ways to minimize costs to sponsors while allowing the agency to ascertain a lack of profitability when that is claimed by the sponsor.

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The requirement that sponsors open their books at reasonable times on demand for examination by FDA-appointed auditors is necessary to enable FDA to verify claims made in orphan-drug designation requests. However, FDA does not expect to exercise the authority to examine companies' books often.

D. Orphan-Drug Exclusive Approval

Section 527 of the act automatically vests a 7-year period of orphan-drug exclusive approval on the date that the agency issues a marketing approval for a designated orphan drug. For this reason, no further action by FDA to bring about exclusive approval is necessary. Under proposed § 316.34, however, the agency would send the sponsor of an approved, designated, orphan drug timely written notice recognizing exclusive approval.

FDA interprets the act to accord exclusive approval only to the first drug approved. This interpretation means that other applicants, who may have invested substantial money and effort in supporting their applications, are barred from marketing for the 7-year period of exclusivity even though they filed before or shortly after the applicant whose product was approved. Because of this, some have argued for "joint exclusivity" between or among "temporally close" competitors, that is, sponsors that submit marketing applications prior to the first approval of the drug.

FDA is required by law to reject the concept of joint or shared exclusivity (unless it is agreed to by all sponsors of a particular drug). The act provides that, after approval of an orphan drug, "* * * [FDA] may not approve another application * * * for such drug for such disease or condition for a person who is not the holder of such approved application * * * until the expiration of seven years from the date of approval of the approved application * * *" (21 U.S.C. 360cc(a)). The agency interprets this language to preclude the possibility of shared or joint exclusivity except where agreed to by the sponsor of the drug with the right to exclusive marketing.

E. Scope of Exclusive Approval

Exclusive marketing is the Orphan Drug Act's primary incentive for the development of orphan drugs. Thus, FDA has intensively considered how it would determine whether one drug is the same as another with respect to orphan-drug exclusive marketing. Historically, any difference in the chemical structure of a drug's active moiety (that part of the molecule other than the parts that make it a salt or ester), whether or not that difference caused a difference in the clinical effect, rendered the drug containing that active moiety a new molecular entity. This distinction antedated any considerations of exclusivity and was principally a classification matter. It reflected the view that the modified drug had a high probability of being different from the original in its actions or toxicity and would need to undergo full toxicologic and clinical testing because it was not possible to tell from examining the structure of the two molecules or performing simple in vitro or in vivo tests whether they would behave identically. FDA was, thus, not prepared to allow "shortcuts" to marketing approval for modified active moieties under any circumstances, no matter what the agency's view of the likely significance of the structural changes and no matter how small they were.

At the same time, it is often possible to modify a small molecule while retaining its desired effect. The ability to do this has been used by sponsors to develop their own versions of popular widely used drugs to avoid infringements of existing patents. Thus, sponsors have in recent years developed modified angiotensin converting enzyme inhibitors, calcium channel blockers, H2-antihistamines, beta-adrenergic blocking agents, steroids, and cephalosporin antimicrobials. While a major aim of the sponsors may have been development of a distinct molecule that would not be restricted by existing patents, sponsors have also been interested in distinguishing their drug therapeutically from a competitor's. The modified molecules were often pharmacologically distinct, sometimes in ways that were quite advantageous, such as by having greater specificity, by lacking a particular adverse effect, or by having different pharmacokinetics.

With respect to small molecules, it appears sound, for the purposes of consideration of exclusive marketing under the Orphan Drug Act, to adopt a policy that regards two drugs as different if they differ with respect to the chemical structure of their active moieties. First, such differences are highly likely to lead to pharmacologic differences. Second, the development of an agent with a novel active moiety is not a financially or intellectually trivial matter; it represents a considerable effort and a substantial risk, as the results of changes in small molecules are difficult to predict.

It would be possible to have the same policy for macromolecules, i.e., to regard any difference in structure, or even any uncertainty about actual structure (e.g., a preparation may contain an array or distribution of closely related molecules or be of such a complex nature that it cannot be precisely defined), as causing two drugs to be considered different. However, the differences in structure/function relationships between macromolecules and small molecules could suggest the need to articulate a different policy for macromolecules.

Some degree of heterogeneity is common in the case of macromolecules; if this were to lead to the conclusion that two products composed of macromolecules were almost always different, there would be little or no exclusive marketing associated with macromolecules, probably not the outcome sought by Congress in enacting the Orphan Drug Act. Also, unlike with small molecules, it is possible to make changes in macromolecules that are very likely to have no pharmacologic effect (e.g., a substitution of one amino acid for another similar one at an unimportant site in the molecule), but that could nonetheless defeat exclusive marketing if any structural difference were sufficient to make drugs different for purposes of orphan-drug exclusive marketing. Again, this is an outcome that might not be consistent with the intent of the Orphan Drug Act.

Because small differences may affect the function of macromolecules much less than that of small molecules, it may be appropriate that certain chemical differences or uncertainties about chemical structure of macromolecules should not cause two drugs to be considered different for purposes of the Orphan Drug Act, unless the chemical differences were associated with improvements in clinical effect. If this policy were implemented, it would be critical to define the kinds of differences in clinical effect that would be considered sufficient to support a conclusion that the drugs were different.

It would be easiest to show that a new drug was different from the innovator drug if any documented pharmacologic difference between the drug were considered a sufficient basis for determining that the drugs were different. Conversely, it would be relatively difficult for a new drug to be considered different if a clear clinical advantage had to be demonstrated.

One can describe several alternative scientifically reasonable sets of criteria for identifying drugs as different for purposes of determining orphan-drug exclusive marketing rights. The crucial differences among them are in how much structural distinction there must be between a drug and a potential competitor and whether the structural

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distinction must be linked to functional differences for the competitor drug to be considered a "different" drug on chemical/structural grounds for purposes of the Orphan Drug Act. In each case, even a drug considered the "same" drug structurally could become a "different" drug for these purposes by showing clinical superiority. Four possible criteria for determining sameness/difference are discussed below:

1. Two drugs would be considered different if they had any defined structural difference (other than being different salts or esters of the same active moiety), such as a different amino acid sequence or glycosylation pattern, or if they had heterogenous structures (e.g., a polysaccharide with an array of molecules having different numbers of the same repeating saccharide unit and thus different chain lengths) or, for other reasons, had a structure that could not be precisely defined.

Comment: This criterion applies similar considerations to small and large molecules. Macromolecular drugs with similar structures and similar, even identical, pharmacologic activity would usually be treated as different drugs. Because it is often not possible completely to define all aspects of the structure of macromolecules, few closely related macromolecules would be considered the same drug, although there would be some cases, for example, two human growth hormones with identical amino acid sequence and no glycosylation, in which identity would be presumed. Using this criterion, orphan-drug exclusive marketing would rarely prevent the development of a competitor macromolecular drug so long as the competitor were willing to support development of a full new drug application (NDA) or product license application (PLA).

2. Two drugs would be considered different if they could be shown to have a defined structural difference, as above. However, they would not be considered different simply because of uncertainty about their precise structure or because the drugs are somewhat indeterminate mixtures. For example, two polypeptide or protein molecules that had the same primary, secondary, and tertiary structures, insofar as could be determined, or had uncertain or mixed chemical structures that could not be distinguished, would be considered the same drug, unless the subsequent drug could be shown to be clinically superior.

Comment: This definition would be very similar to criterion 1 in practice, although it would be slightly more likely that competing products would be considered the same drug. The definition itself would create a strong incentive for sponsors to identify and define structural differences in previously indeterminate macromolecules, either through additional testing or minor manipulations in structure.

3. Two drugs would be considered the same drug if the principal, but not necessarily all, structural features of the two drugs were the same, unless the subsequent drug were shown to be clinically superior. This criterion would apply as follows to different kinds of macromolecules:

a. Two protein drugs would be considered the same if the only differences in structure between them were due to: (1) Post-translational events; or (2) infidelity of transcription or translation; or (3) minor differences in amino acid sequence. Other potentially important differences, such as different glycosylation patterns or different tertiary structures, would not cause the drugs to be considered different unless the subsequent drug were shown to be clinically superior.

b. Two polysaccharide drugs would be considered the same if they had identical saccharide repeating units, even if the number of units were to vary and even if there were post-polymerization modifications, unless the subsequent drug could be shown to be clinically superior.

c. Two polynucleotide drugs consisting of two or more distinct nucleotides would be considered the same if they had an identical sequence of purine and pyrimidine bases (or their derivatives) bound to an identical sugar backbone (ribose, oxyribose, or modifications of these sugars) unless the subsequent drug were shown to be clinically superior.

d. Closely related complex partly definable drugs with similar therapeutic intent, such as two live viral vaccines for the same indication, or some other traditional biological, would be considered the same unless the subsequent drug were shown to be clinically superior or to depend on different mechanisms of action.

Comment: This criterion makes a presumption of sameness, even in the case of proteins, in the face of minor differences in structure other than differences in the primary amino acid sequence if those differences occur after the basic amino acid change is translated from the RNA. Sameness is also presumed even in the face of amino acid sequence differences if they are "minor".

Determining whether differences in amino acid sequences should be considered minor involves judgment and could lead to legal challenges of FDA decisions. An alternative approach would be to allow any difference in amino acid sequence to cause a molecule to be considered different. With that approach, however, a second sponsor could then introduce an inconsequential difference in amino acid sequence solely to defeat orphan-drug exclusion marketing. Overall, the approach embodied in criterion 3 would, compared to the first two approaches, tend to increase the likelihood that a potential competitor would be barred by the Orphan Drug Act from marketing a variant of an already marketed orphan drug.

4. Two similar macromolecules would be considered the same unless their structures differed in ways that could reasonably be expected to influence relevant pharmacologic activity. Other structural differences would not cause the second drug to be considered a different drug unless the subsequent drug were shown to be clinically superior.

Comment: Like criterion 3, this approach makes a relatively strong presumption of sameness for pharmacologically related drugs and would support orphan-drug exclusive marketing of the first approved drug in the face of considerable differences in structure. This approach depends even more than does criterion 3 on judgment in that the kinds of structural differences likely to be related to differences in pharmacological activity are not specified. However, in this case, the agency would have to determine that a particular structural change was likely to be associated with a clinical difference without necessarily requiring evidence from clinical studies that it actually did lead to such a difference. This would entail making a complex and potentially controversial judgment.

All of the above four criteria are scientifically reasonable, and selection of one involves policy considerations as much as scientific ones. Criteria 1 and 2 use the same criteria for determining differences between macromolecules that are used to determine whether small, well-defined drugs have the same active moieties. Criteria 3 and 4 are based on the premise that function of macromolecules is less directly related to minor structural differences than is the case for small molecules and incorporates an assessment of functional relevance into the comparisons.

The first two criteria give relatively little value to orphan-drug exclusive marketing for macromolecules, allowing any evidence of structural difference, or

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uncertainty about structure, to cause two drugs to be considered different drugs. They are fairly easy to interpret. The subsequent drug sponsor would not get a free ride, as it would still have to carry out the studies necessary to support its own marketing application, a significant effort. However, that subsequent sponsor could proceed with a reasonably sure expectation of ultimately being able to market the drug.

The third criterion, which FDA is proposing to adopt, gives considerable protection to the first approved orphan product against a second sponsor's attempts to defeat exclusive marketing rights by introducing minor molecular changes. It would also be reasonably straightforward to implement; minor chemical differences simply would not cause a subsequent drug to be considered different unless the subsequent drug were shown to be clinically superior. FDA is proposing this option because it would seem to constitute the best available mechanism to protect the integrity of the chief incentive for orphan drug development that Congress created while allowing clinically superior drugs with similar chemical structure to be marketed. Criterion 4 leaves so much to discretion that day-to-day implementation could become a major problem. Choice of criterion 3 is consistent with discussions at the Institute of Medicine meeting held on November 19 and 20, 1990.

Under the test set forth under criterion 3, a drug would be considered different if it were shown to be clinically superior to an already approved orphan drug. FDA proposes that a drug be considered "clinically superior" to an already approved orphan drug when it provides a therapeutic advantage for at least one of the following three reasons:

(1) It has greater effectiveness than the approved orphan drug (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative effectiveness claim for two different drugs. In most cases, direct comparative clinical trials would be necessary; or

(2) It has been shown to be safer in a substantial portion of the target population, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. Superior safety might also be proven where two drugs have approximately the same therapeutic effect but where the subsequent drug is shown to produce that effect at a lower dose and only where the first drug had significant side effects. In some cases, direct comparative clinical trials would be necessary; or

(3) In unusual cases, where the subsequent drug has not been shown to be safer or more effective, a subsequent drug could nevertheless qualify as being "clinically" or "therapeutically" superior through a demonstration that the product otherwise makes a major contribution to patient care.

This third basis for finding a subsequent drug to be clinically superior is intended to constitute a narrow category, and its proposed use is not intended to open the flood gates to FDA approval for every drug for which a minor convenience over and above that attributed to an already approved orphan drug can be demonstrated. The only situation that FDA has identified as potentially providing a "major contribution to patient care" without a clear showing of a gain in safety and/or effectiveness is the development of an oral dosage form where the first drug was available only in a parenteral dosage form. FDA solicits comments as to whether other kinds of differences, such as differences in method or vehicle of administration, might constitute "major contributions to patient care." Because FDA has not been charged with making decisions on the approval of drugs based on cost, the agency proposes to rule out cost considerations in determining whether a drug makes "a major contribution to patient care."

It has been suggested that, whenever FDA is asked to approve a subsequent drug because it is "clinically superior" to the first-approved drug, the agency should give the sponsor of the first drug an opportunity to conduct studies showing that its drug matches the superior qualities of the subsequent drug. FDA proposes to reject this suggestion on grounds that it is not fair to the sponsor of this similar but nevertheless innovative drug to refuse to allow this subsequent sponsor the fruits of its testing and research. Also, giving the first sponsor this opportunity might delay the approval of a clinically superior drug, especially where the first sponsor is significantly behind in testing the clinically superior drug.

In any situation where FDA confronts a question of whether or not a subsequent orphan drug is the same as or different from an already approved first orphan drug, FDA proposes to place the burden of proof (including the burden of production of evidence and the burden of persuasion of FDA) on the sponsor of the subsequent drug who is contending that its drug is different. It is usual for FDA to require a sponsor to prove all aspects of its entitlement to market a product. Applied here, such a rule would better protect the integrity of the chief incentive that Congress created for orphan-drug development than would the placing of the burden on the exclusive marketing holder.

F. Inadequate Supplies

Under section 527 of the act, whenever the agency (and by delegation under 21 CFR 5.58(b), the Director, Office of Orphan Products Development (OOPD)) has reason to believe that the holder of an approved marketing application cannot assure the availability of sufficient quantities of an orphan drug to meet the needs of people with the disease or condition for which it was designated an orphan drug, the act provides that the agency may approve another application for the same drug for the same indication.

Proposed § 316.36 provides a procedure whereby the Director, OOPD, would notify the holder of the possible insufficiency and would request, within a specified time, that the holder (1) provide in writing or orally or both, at the Director's discretion, views and data as to how the holder can assure the availability of sufficient quantitites of the drug; or (2) consent to the approval of other marketing applications.

Following his or her decision in the matter, the Director would issue an order with findings and conclusions, either reaffirming or withdrawing the drug product's exclusive approval. Any such order which the Director issues would constitute final agency action. In the event the Director's decision is to withdraw the drug product's exclusive approval, FDA may approve any number of marketing applications even if the additional applicants cannot themselves assure the availability of sufficient quantities of the orphan drug in question. Congress' clear intent was to foster the development and marketing of sufficient supplies of drugs for rare diseases (H. Rept. 97–840, 97th Cong. 2d., p. 7, 1982). Marketing approvals of other sponsors' drugs would encourage orphan drug development even if the new marketing approval holder could not itself immediately guarantee adequate supplies either by itself or with other manufacturers.

Once exclusive marketing is broken under section 527 of the act for failure to assure the availability of adequate supplies, it cannot be restored even if the first manufacturer is later able to assure the availability of adequate supplies. It would be unreasonable to expect a second manufacturer to make a large investment in drug development to fill a gap if it could be shut out of the

HeinOnline -- 56 Fed. Reg. 3343 1991

market at any time that the original manufacturer could assure adequate supplies.

G. Open Protocols

In subpart E of proposed part 316, FDA commits itself to encourage sponsors of designated orphan drugs to design and implement treatment protocols to permit treatment of any patient with the rare disease or condition during investigations of the drug upon request by the patient's physician. FDA notes that, in FDA's experience to date, the vast majority of orphan drugs under investigation are being tested for "serious" or "immediately life-threatening" diseases as they are defined in 21 CFR part 312, and proposed § 316.40 so provides.

H. Availability of Information

FDA recognizes that designation requests will contain confidential commercial information and, indeed, that the very existence of an orphan-drug designation request may itself be confidential commercial information. In addition, a request for orphan-drug designation is in most instances supported by information that will be incorporated in a sponsor's marketing application. Release of such information prior to marketing approval of the sponsor's drug product could have an adverse impact on the sponsor's obtaining first approval and, thus, exclusive approval pursuant to section 527 of the act.

For all these reasons, proposed § 316.52(a) provides that no information submitted by a sponsor as part of a request for orphan-drug designation would be released by FDA to the public prior to such time as FDA takes final action on the request. This means that unless previously disclosed or acknowledged, FDA would not make public the existence of any pending orphan-drug designation request. Under proposed § 316.52(c), however, upon granting orphan-drug designation, FDA would publish the following information: the trade and generic names of the designated product, the uses for which the drug is designated, the date of the granting of orphan-drug designation, and the name and address of the sponsor of the drug receiving designation.

Proposed § 316.52(b) provides that, irrespective of whether the existence of a pending request for designation has been publicly disclosed or acknowledged, no data or information in the request are available for public disclosure prior to final FDA action on the request. Upon final FDA action on a request for designation, proposed § 316.52(c) provides that FDA will determine the public availability of data and information in the request in accordance with 21 CFR parts 20 and 21 CFR 314.430.

In accordance with proposed § 316.52(e), FDA will follow existing statutes and regulations in deciding whether to disclose publicly the existence of a pending marketing application for a designated orphan drug for the use for which the drug was designated. In general, FDA does not disclose the existence of the application unless it has been previously publicly disclosed or acknowledged or disclosure is otherwise required. Finally, proposed § 316.52(f) provides that FDA will determine the public availability of data and information contained in pending and approved marketing applications for a designated orphan drug for the use for which the drug was designated in accordance with part 20, § 314.430, and other applicable requirements.

I. Administrative Challenge Procedures

FDA does not propose to provide for a hearing on issues of the scope of exclusive approval or any other issues of approvability or orphan-drug designation under the Orphan Drug Act. Neither the Constitution, nor the Administrative Procedure Act, nor the Orphan Drug Act requires a hearing on any issue of this kind. Hearings are time-consuming and resource-intensive. FDA is not persuaded that a regulatory hearing before the agency under part 16 of FDA's administrative practices and procedures regulations (21 CFR part 16) is more likely to lead the agency to a correct result than is careful administrative review. Further, the agency notes that, if a challenging sponsor has sufficient information, it can, under current regulations, mount an effective challenge to an incipient drug approval by filing a citizen petition pursuant to 21 CFR 10.30.

FDA considered creating an administrative procedure, without a hearing, whereby the agency would give notice to the sponsor of an approved exclusively marketed orphan drug of the proposed approval of another sponsor's application for marketing a drug that, in FDA's view, is similar but not identical. Further, FDA considered the possibility of allowing the sponsor of the exclusively marketed drug an opportunity to challenge administratively the proposed approval of a subsequent drug.

FDA has decided not to propose a new administrative procedure for allowing challenges to incipient marketing application approvals or denials under section 527 of the act. Just as there is no requirement for a hearing, there is no requirement in the Constitution, the Administrative Procedure Act, or the Orphan Drug Act for such an administrative procedure. Also, postdecisional judicial review is preferable to an administrative challenge procedure because a predecisional challenge procedure would be time consuming and could be used for the sole purpose of delaying approval of competing drugs. Also, it would be difficult to determine who should have the right to challenge an incipient approval and who should be entitled to what notice of what anticipated agency action. Finally, a predecisional administrative challenge procedure would present difficulties due to the nondisclosability of relevant information under FDA's public information regulations (21 CFR part 20 and other regulations cited in that part).

For these reasons, FDA believes that the disadvantages of an administrative challenge procedure are too great to justify creating one.

J. Economic Impact

The agency has examined the economic impact of this proposed rule in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354) and concludes that this proposed rulemaking is not a major rule as defined by Executive Order 12291 and will not have a significant impact on a substantial number of small entities.

The proposed rule would codify existing administrative practices that implemented the Orphan Drug Act of 1983 and its amendments. Because the proposed rule introduces no new requirements, it imposes no incremental costs on industry or consumers.

It is clear that the Orphan Drug Act, as implemented by existing administrative practices, has significantly increased the rate at which new orphan drugs are marketed. While two or three drugs that might be eligible as orphan drugs were approved annually prior to the Orphan Drug Act, an average of eight designated orphan drugs have been approved per year and marketed since 1984. Moreover, orphan-drug designation has been granted to an average of 41 drugs per year since 1984. Thus, the Orphan Drug Act, as implemented since 1983, has provided an effective stimulus for the development and marketing of drugs for diseases or conditions that are rare in the United States.

K. Environmental Impact

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

HeinOnline -- 56 Fed. Reg. 3344 1991

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

L. Paperwork Reduction Act of 1980

This proposed rule contains information collections which are subject to review by the Office of Management and Budget (OMB) 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: Orphan Drug Regulations—NPRM.

Description: These proposed regulations specify the procedures for sponsors of orphan drugs to use in availing themselves of the incentives provided for in the Orphan Drug Act and set forth the procedures FDA would use in administering it.

Description of Respondents: Businesses or other for-profit organizations.

ESTIMATED ANNUAL REPORTING AND RECORDKEEPING BURDEN

Section	Annual number of respondents	Annual frequency	Average burden per response	Annual burden hours
316.10	6	1	125	750
316.20 and 316.21	28	1.78	125	6,250
316.22	3	1	2	6
316.27	5	1	4	20
316.36	1	3	15	45
Total				7,071

The agency has submitted a copy of this proposed rule to OMB for its review of these information collections. Comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, may be submitted to FDA's Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, OMB, Washington, DC 20503.

M. Effective Date

FDA proposes that any final rule based on this proposal would become effective 30 days after the date of publication of the final rule.

N. Request for Comments

Interested persons may, on or before April 1, 1991, submit to the Dockets Management Branch (address above) written comments regarding this proposal. 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. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 316

Orphan drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act, it is proposed that 21 CFR part 316 be added as follows:

PART 316—ORPHAN DRUGS

Subpart A—General Provisions

Sec.

Subpart B—Written Recommendations for Investigations of Orphan Drugs

Subpart C—Designation of an Orphan Drug

Subpart D—Orphan-drug Exclusive Approval

Subpart E—Open Protocols for Investigations

Subpart F—Availability of Information

Authority: Sections. 525, 526, 527, 528, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360aa, 360bb, 360cc, 360dd, 371).

Subpart A—General Provisions

§ 316.1 Scope of this part.

(a) This part implements sections 525, 526, 527, and 528 of the act and provides procedures to encourage and facilitate the development of drugs for rare diseases or conditions, including biological products and antibiotics. This part sets forth the procedures and requirements for:

(1) Submissions to FDA of:

(i) Requests for recommendations for investigations of drugs for rare diseases or conditions;

(ii) Requests for designation of a drug for a rare disease or condition; and

(iii) Requests for gaining exclusive approval for a drug product for a rare disease or condition.

(2) Allowing a sponsor to provide an investigational drug product under a treatment protocol to patients who need the drug for treatment of a rare disease or condition.

(b) This part does not apply to food, medical devices, or drugs for veterinary use.

HeinOnline -- 56 Fed. Reg. 3345 1991