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: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing final 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 act). In the **Federal Register** of January 29, 1991 (56 FR 3338), the agency proposed regulations to implement this section of the Orphan Drug Act. The Orphan Drug Act directs FDA to provide written recommendations on studies required for approval of a marketing application for an orphan drug. It also 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 marketing approval. 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. This action will benefit consumers by encouraging manufacturers to develop and make available to patients drugs for diseases and conditions that are rare in the United States.

EFFECTIVE DATE: January 28, 1993.

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:

I. Background

In enacting the Orphan Drug Act (Pub. L. 97-414), Congress required FDA to issue regulations for the implementation of sections 525 and 526 (21 U.S.C. 360aa-360bb) that the Orphan Drug Act added to the act. These sections relate to written FDA recommendations on studies required for approval of marketing applications for orphan drugs and for the designation of eligible drugs as orphan drugs. Accordingly, in the **Federal Register** of January 29, 1991 (56 FR 3338), FDA issued a notice of proposed rulemaking entitled "Orphan Drug Regulations" for the implementation of these sections as well as for the implementation of sections 527 and 528 of the act (21 U.S.C. 360cc-360dd), which relate to exclusive marketing for orphan drugs and the encouragement of sponsors to make orphan drugs available for treatment on an "open protocol" basis before the drug has been approved for general marketing. This notice of proposed rulemaking will hereinafter be referred to as the "NPRM."

FDA announced that the proposed regulations codified existing administrative practices implementing the Orphan Drug Act as amended. The agency noted that the proposed regulations would, where possible, attempt to ensure that the act's incentives were available only when they would further the purposes of the Orphan Drug Act and that the act should never be used to block significant improvements in the treatment of rare diseases.

II. Summary of and Response to Comments

In response to FDA's NPRM, the agency received 40 public comments. Most comments came from either companies or trade associations of companies that are marketing or hope to market orphan drugs and from two associations representing patients with rare diseases or conditions. FDA has responded to all comments that were received and filed in FDA's Dockets Management Branch. Most comments are considered in the numerical order of the proposed sections to which they are related.

A. General Comments on the Preamble

1. One comment addressed the following statement in the Preamble: "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." (See NPRM, section II.B., paragraph 18). The comment expressed the fear that the prospective-only application of the regulation might mean that FDA would be unable to approve a clinically superior subsequent drug otherwise identical to a pioneer that had been approved and obtained orphan drug exclusive marketing prior to the effective date of this rule.

FDA advises that the fear expressed in the comment is groundless. FDA meant only to rule out reconsideration of previous drug designation and approval decisions. FDA did not mean that it would refuse to approve a clinically superior drug that might not have been approvable prior to promulgation of this rule.

2. Another comment objected to the use of the proposed rule as operational policy prior to issuance of final regulations. The comment argued that the final rule should not apply retrospectively to drugs that held orphan designation prior to the effective date of the final rule.

FDA has not relied on the proposed rule to dictate operational policy during the interim period between the publication of the NPRM and the publication of this final rule. However, FDA decision's during this period have as a matter of fact been consistent with the provisions of the proposed rule. As to retrospective application of the proposed rule, FDA does not regard the application of these regulations to already designated drugs as a retrospective application as long as FDA does not reconsider previous decisions concerning these drugs.

3. One comment stated that designated orphan drugs should be exempt from all investigational new drug application (IND), new drug application (NDA), product license application (PLA), and Establishment License Application (ELA) user fees, as user fees for review of these drugs would be inconsistent with the intent of the Orphan Drug Act.

FDA advises that the question of user fees is outside the purview of this regulation. However, in the future, when and if user fees are considered, designated orphan drugs will be considered for exemption from them.

4. Several comments urged that marketing applications for drugs whose approvals are temporarily barred by the exclusive marketing provisions of the Orphan Drug Act nevertheless be completely reviewed so that they may be quickly approved upon the expiration of the 7 years' exclusive marketing period.

FDA advises that, once the agency determines that approval of a drug would be temporarily barred by the exclusive marketing provisions of the Orphan Drug Act, the timing of the review will be decided on a case-by-case basis by the appropriate division of the Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research. Such decisions will be based on time and resource considerations as well as on

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the complexity of information to be considered.

5. Some comments argued that the proposed regulations go too far in protecting exclusive marketing rights, while other comments argued that they do not go far enough.

On the whole, based on the legislative history of the Orphan Drug Act and FDA's understanding of its purposes, the agency came to its conclusions by seeking as much as possible to protect the incentives of the Orphan Drug Act without allowing their abuse. FDA believes the final rule achieves the best balance possible between protecting exclusive marketing rights and fostering competition.

B. Sameness Versus Difference

6. One comment suggested that proposed § 316.3(b)(3)(ii) be amended to include a reference to "severe" adverse reactions in addition to "frequent" adverse reactions. Another comment suggested substituting the word "meaningful" for "substantial" in the same paragraph and substituting the phrase, "clinically significant adverse effects" for "relatively frequent effects."

FDA has carefully considered the suggested changes and concludes that it will not amend the final rule as requested because the proposed changes would not add to the clarity of the regulation. The use of the words, "frequent," "meaningful," and "relatively frequent adverse effects" are intended as examples of considerations that might be relevant in determining clinical superiority and are not intended as the only routes to demonstrating greater safety of a drug. FDA's decision not to use the suggested words and phrases does not mean that FDA would not consider less severe adverse reactions in a meaningful portion of the target population or a diminution of clinically significant adverse effects as being evidence of greater safety.

7. One comment pointed out that § 316.3(b)(13)(i) and (b)(13)(ii) should both use the phrase, "intended for the same use," which was used in proposed § 316.3(b)(13)(i) but was omitted from paragraph (b)(13)(ii).

FDA agrees, and the phrase, "intended for the same use," which was inadvertently omitted, has been added to § 316.3(b)(13)(ii).

8. Another comment stated that § 316.3(b)(3)(i) refers to "the same kind of evidence to support a comparative effectiveness claim for two different drugs." The comment asked that FDA make clear that the standard in the NPRM will be consistent with FDA's prescription drug advertising standard, which requires a showing of clinical significance of the claim.

FDA believes that it is more accurate to draw a comparison between the clinical superiority standard in this rule with FDA's standards for use of such claims in prescription drug labeling found in 21 CFR 201.57(c)(3)(v) (as distinguished from drug standards for advertising).

9. Several comments asked that examples be provided and the difference between "minor" and "major" convenience be clarified as stated in the NPRM preamble statement (section II.E. (56 FR 3341 at 3343)) "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."

FDA does not believe that it can anticipate all or even most possible bases for categorizing some contributions as major and others as minor. Each will vary with the facts. Hence, examples could be as misleading as they could be helpful.

10. Another comment proposed that the concept of "active moiety" be applied to macromolecular products as well as to micromolecular products and that differences in active moieties by themselves be used as the sole criterion for establishing product differences.

FDA disagrees, because it does not believe that the concept of active moiety, as used for small molecules, is useful for macromolecular entities. For micromolecular products, the active moiety is the whole covalently bound part of the molecule that is active. This means that it generally consists of all of the molecule except added parts that make it a salt or ester. Essentially, any change in covalent structure creates a new active moiety whose properties may well differ from the old active moiety. With macromolecules, it would be trivially easy to make minor covalent changes that would leave the activity of the drug unaltered, but would create a "different drug" if the micromolecular definition of active moiety were to be used. This would render exclusive marketing of macromolecular drugs meaningless and would decrease incentives to develop orphan drugs. When such a change is meaningful, of course, it deserves, and under the rule would gain, exclusive marketing.

11. A comment suggested that FDA should assume that macromolecular drugs made by different manufacturers are by definition different.

FDA strongly disagrees, because this would result in a de facto exclusion of all biological products from eligibility for exclusive marketing rights, the major incentive of the Orphan Drug Act. Regardless of how similar they were to each other, each sponsor's drug would be entitled to exclusive marketing, or, put another way, would not be kept from marketing by the exclusive marketing status of the prior drug, rendering such status meaningless for these drugs. Because macromolecules, and particularly recombinant products, offer great promise for the diagnosis and treatment of rare diseases and conditions, and because FDA does not believe that Congress intended to eliminate them from the operation of the Orphan Drug Act's exclusive marketing incentive, FDA will not consider every drug manufactured by a different manufacturer to be different for purposes of the act. This matter was fully discussed in the preamble to the NPRM (56 FR 3341 through 3343.)

12. Another comment suggested that the rule should define the term, "arbitrary," (as used in the NPRM, section II.B (56 FR 3339)) and provide examples for greater ease in determining what is "salami slicing" or artificial and medically implausible subsets.

FDA believes that the term "arbitrary" needs no further explanation. The NPRM by implication defines the term "arbitrary" as "medically implausible." Setting forth examples could mislead as easily as it could assist because every FDA decision on arbitrariness would necessarily be highly fact dependent.

13. A comment proposed that:

> * * * closely related, complex partly definable drugs with similar therapeutic intent be considered the same if they are derived from the same source and manufactured by a similar process, such as two live viral vaccines for the same indication, would be considered the same drug unless the subsequent drug were shown to possess different quantitive in vitro biologic activity or to be clinically superior.

FDA disagrees. Whereas a difference in in vitro quantitative biologic activity may constitute part of the evidence needed to support a claim of clinical superiority, it will not normally suffice for that purpose. Because such differences do not all correlate with clinical superiority, if no such correlation is independently proven with respect to an orphan drug, no meaningful difference for purposes of the Orphan Drug Act will have been shown. In addition, FDA sees no significance for purposes of the Orphan Drug Act with regard to the source from which the drugs are derived and the processes by which they are

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manufactured, unless such factors lead to clinical superiority.

14. Another comment suggested that the NPRM preamble could be read to indicate that glycosylation is not a post-translational modification.

FDA certainly did not intend such a meaning and takes this opportunity to make clear that it views glycosylation as a post-translational modification.

15. The comment addressed in the previous paragraph also stated the view that, under the proposed rule, clinical superiority will always lead to approval of a subsequent drug.

FDA agrees with the comment's viewpoint. Assuming that a subsequent drug's marketing application is otherwise approvable, FDA will not interpret the Orphan Drug Act to block approval of any drug proved to be clinically superior to a drug with currently effective exclusive marketing rights.

16. One comment noted a disparity between: (1) FDA's firmness in requiring comparative clinical trials to demonstrate greater efficacy, and (2) FDA's stated intent to enforce such a requirement only "in some cases" to demonstrate safety.

FDA agrees that reliable information on safety differences may require comparative trials. Valid safety information may, however, come from other sources as well; the agency believes that the requirements for approving a drug because it is safer than an approved orphan drug may not always need to include the conduct of comparative clinical trials.

17. Two comments questioned why FDA treats micromolecular drugs and macromolecular drugs differently.

As discussed in comment 10, and in detail in the NPRM, FDA does not believe that the concept of active moiety, which has been useful when applied to micromolecular drugs, is adequate to deal with the different situation that obtains with macromolecular drugs.

18. Two comments challenged the use of the concept of clinical superiority, contending that the criteria for demonstrating it are insufficiently clear. Also, the comments noted that, to a sick patient, removing even a minor adverse reaction can result in clinical superiority.

FDA agrees that a small demonstrated improvement in efficacy or diminution in adverse reactions may be sufficient to allow a finding of clinical superiority. Despite the agency's inability to define "clinical superiority" as precisely as some would like, the agency believes that it is a useful concept.

FDA also believes that it constitutes the best tool for giving effect to the intent of Congress to provide incentives for potential sponsors to develop safer and more effective orphan drugs.

19. A comment suggested that, as proof of clinical superiority, FDA should always require a demonstration of it in rigorous double-blind, head-to-head comparative clinical trials such as those required to support other comparative safety and efficacy claims. Such studies, according to the comment, should be done using the licensed product and the subsequent product formulated with the same biologically active units and the same excipients.

While randomized double-blind, concurrently controlled clinical trials are usually the most reliable sources of evidence, other kinds of studies can be considered adequate and well-controlled studies within the meaning of (21 CFR 314.126) to support a finding of clinical superiority. This final rule should not preclude that possibility even if concurrently controlled trials will usually be needed. As stated, the kinds of data needed to demonstrate clinical superiority for purposes of the Orphan Drug Act will be the same as the kinds of data required to allow label claims of superiority.

20. Two comments suggested that, for drugs indicated for acquired immunodeficiency syndrome (AIDS) and other similar serious diseases, a lower does with little or no loss of effectiveness should qualify the drug as clinically superior.

FDA believes that a lower dose per se, without diminution of side effects or enhanced patient convenience should not constitute clinical superiority for purposes of this rule.

21. One comment argued that a subsequent drug should not be approved unless the subsequent drug is shown to be both "materially different" and clinically superior. Specifically, the comment stated, peptides which mimic the active sites of a protein drug should not be considered different from the protein drug.

FDA advises that, under "criterion 3," which states that "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" (NPRM, section II.E. (56 FR 3341 through 3342)), which the agency is adopting, either differences in active moiety or clinical superiority will be sufficient to make two micromolecular drugs different. With regard to macromolecular drugs, clinical superiority by itself will render a subsequent drug different. However, even if clinical superiority cannot be proven, macromolecular drugs may be different because of major differences in molecular structure apart from post-translational events. In other words, FDA believes that there are certain major differences in the chemical composition of drugs that make them different for purposes of the Orphan Drug Act regardless of whether they produce different clinical responses.

As to the peptide example, in order for a peptide that resembles a portion of a protein product to be considered a different drug, FDA will require a clear demonstration that the peptide is clinically superior to the entire protein.

22. One comment suggested that the final rule must state how much superiority would represent a major contribution to patient care.

There is no way to quantify such superiority in a general way. The amount and kind of superiority needed would vary depending on many factors, including the nature and severity of the disease or condition, the quality of the evidence presented, and diverse other factors.

23. Another comment argued that the concept of clinical superiority is neither supported by the act nor appropriately defined. Further, the comment argued that direct comparative clinical trials usually needed to demonstrate clinical superiority would be difficult because subjects would be scarce, the time to perform the trials would exceed the period of exclusive marketing, and the cost would be prohibitive.

Congress left it to FDA to define "such drug" as used in 21 U.S.C. 360cc and provided no guidance on the meaning of this term. Thus, it is within FDA's authority to define what is the "same" and what is a "different" drug. "Clinical superiority" is a rational and permissible means of making this distinction. FDA understands the difficulties inherent in proving clinical superiority but believes the requirement is necessary in order to protect the value of the primary incentive that Congress created in the Orphan Drug Act. If FDA allows exclusive marketing rights to be eliminated without evidence of clinical superiority or based on shoddy evidence, the incentive will be worthless.

24. Several comments argued that FDA must recognize the effect of price on access to patient care and urged that cost considerations must be used in determining whether a subsequent drug makes a major contribution to patient care. On the other hand, several other comments stated that cost should not be a factor in decisions about whether a

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drug represents a major contribution to patient care.

FDA agrees with the latter comments. Although FDA understands that costs can indeed have a major impact on access to a drug, FDA has no authority over drug pricing or any authority to consider it in drug approval. Further, considering price as a factor in whether or not a drug makes a major contribution to patient care is problematic. If FDA could approve a drug because its relatively low cost were deemed to constitute a major contribution to patient care, there would be no effective tool that FDA could use to prevent the sponsor of the subsequent drug from quickly raising its price to the level of its competitor's price after approval.

25. Several comments suggested that FDA should liberally construe the concept, "major contribution to patient care." These comments advanced the following examples of factors that the comments would have the agency consider: convenient treatment location; duration of treatment; patient comfort; improvements in drug efficiency; advances in the ease and comfort of drug administration; longer periods between doses; and potential for self administration.

FDA agrees that these factors, when applicable to severe or life-threatening diseases, might sometimes be legitimately considered to bear on whether a drug makes a major contribution to patient care. However, this determination will have to be made on a case-by-case basis.

26. In contrast to the previous comments, three comments argued that the concept of "major contribution to patient care" should be narrowly construed so that only truly important differences could result in a finding of a "major contribution" if greater safety and/or effectiveness are not involved. The comments urged that minor improvements in patient convenience, such as a change that allows for home use of a drug for the first time, or "political considerations" should not qualify and that, in any case, head-to-head comparative clinical trials should be required.

Home use or improved patient access may or may not constitute a major contribution to patient care, depending on the drug and the nature of the disease, among other things. While comparative trials are, of course, preferred and will usually be required, it is possible that, in some circumstances, a demonstration of a major contribution to patient care can be made without such trials.

27. Several comments argued that a subsequent drug should be deemed to be clinically superior to the first approved drug if its delivery system results in enhanced compliance among patients who would otherwise experience compliance difficulties. Examples provided for variations in drug delivery warranting such a finding included: novel inhalation therapy; oral, intranasal, inhalational, transdermal vehicles of administration where intravenous means were once all that was available; innovative time-release delivery mechanisms; the availability of an improved delivery system that eliminates the risk of hemophilia B; and a new parenteral administration that permits once-a-day administration rather than four-times-a-day injections or infusions.

FDA agrees that a change in drug delivery systems might in some cases constitute a major contribution to patient care, but this can only be decided on a case-by-case basis, considering the nature of the disease or condition, the nature of the drug, the nature of the mode of administration, and other factors.

28. Three comments stated that investigational drugs that are significantly purer than approved drugs should be considered clinically superior without comparative clinical trials. An example provided was investigational factor IX products, which are 90 percent factor IX as compared to currently marketed factor IX products, which are only 10 percent factor IX.

If sponsors provide evidence to demonstrate that an improvement in purity will cause a drug to meet one or more of the criteria for clinical superiority, FDA will consider such evidence, which should normally include comparative clinical trials.

29. A comment argued that the NPRM ignores the precedent set in *Genentech* v. *Bowen and Young*, 676 F. Supp. 301 (D.D.C. 1987), in which the court allegedly held that one amino acid difference made a different drug. The comment argued that the final rule should reflect this alleged holding in order to allow FDA to fend off future legal challenges.

FDA disagrees with the comment's characterization of the *Genentech* v. *Bowen and Young* holding. In that case, the court held only the orphan-drug designation of a subsequent drug during the pioneer's period of exclusive marketing was lawful because the subsequent drug was of synthetic origin and did not present the danger of contamination with disease that the pioneer, which was manufactured from human cadavers, did. Although in that case it was argued that one amino acid difference made a different drug, the court never so held. For reasons described above (see comment 10) and in the NPRM, FDA has not adopted this principle in the final rule.

30. One comment suggested that differences in those parts of macromolecules demonstrated to be important for function should form the basis for determining whether two given molecules are different.

Although some changes in critical parts of the molecule, e.g., in the primary structure at the active site, would alter the function of the macromolecule, FDA does not agree that any change in the part of a molecule important for function should be considered a basis for defining a drug as different. Many changes, even in those parts of the molecule, would be of no significance. The agency believes that the changes that are of significance can be evaluated in preclinical laboratory and animal studies and in clinical trials, and, if they show promise of causing a chemically significant difference, the sponsor can develop the drug and demonstrate the difference. A showing of such a difference would represent a basis for approving the drug as a different drug.

31. Another comment urged FDA to develop a guidance document describing differences in amino acid sequence of a protein which would be considered "minor."

FDA declines to set forth hypothetical situations of the kind asked for, as such determinations will be highly fact-dependent.

32. One comment urged that function should play some role in defining when drugs composed of protein are the same. When drugs show similar qualitative activity that appears related to their effectiveness, in vivo or in vitro, the comment said, and the amino acid sequence of the subsequent product is coincident with that of the pioneer, the drug should be considered the same drug.

FDA agrees with the comment generally. Under the criterion 3 proposed for adoption in the NPRM (see comment 21), drugs with similar qualitative activity and similar amino acid sequence would not be considered different from the pioneer unless some clinical superiority could be demonstrated.

33. One comment urged that FDA should deem a drug different from the pioneer if FDA would require a full NDA with original supporting data before approving the subsequent drug. The comment found this approach preferable to "FDA's proposed mixture

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of sometimes relying on physical structure, sometimes relying on functional effect, sometimes refusing to consider functional effect, and making presumptions about whether particular physical structures are likely to have a functional effect * * *."

In developing the NPRM, FDA considered deeming drugs to be different if the agency would normally require a full NDA or PLA with original supporting data before approving the subsequent drug. However, such a rule would make it too easy to break exclusive marketing by making small modifications in molecular structure or in the drug's indications, changes that would usually trigger a requirement for a full NDA. Indeed, for many complex macromolecular products, there is no degree of similarity that would lead to approval of an application without a full NDA or PLA. This would mean that most macromolecules would be ineligible for exclusive marketing rights, an outcome that, for reasons described above, does not seem compatible with the purpose of the Orphan Drug Act.

34. One comment requested that FDA make available the report of the Institute of Medicine, National Academy of Sciences (IOM) concerning issues discussed in section II.E. of the NPRM, i.e., reasonable criteria for identifying drugs as different for purposes of determining orphan-drug exclusive marketing rights.

The report of this workshop, held on November 19, 1990, is available from National Academy Press (Report of a Workshop, "Microheterogeneity of Biological Macromolecules," Forum on Drug Development, 1991. Division of Health Science Policy, Institute of Medicine, National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418).

As was mentioned in the preamble to the proposed rule (56 FR 3338 at 3343), FDA's choice of the third criterion (NPRM, section II.E. (56 FR 3338 at 3341 through 3342)) in the NPRM and in this final rule is consistent with the discussions at the IOM's "Workshop on Microheterogeneity of Biological Macromolecules."

C. Written Recommendations for Investigations of Orphan Drugs

35. One comment expressed a view that information on the current regulatory and marketing status and history of the drug product that the sponsor is required to submit under proposed § 316.10(b)(7) should be specific only to the sponsor's regulatory and marketing activities.

In order to provide useful recommendations on the studies necessary to support marketing approval of a drug, FDA needs whatever information is known or accessible to the sponsor concerning approved indications, recalls, adverse experience, other uses, abuse potential, etc., on the drug. This would include both the sponsor's regulatory and marketing activities and those of others about which the sponsor knows or could reasonably find out about.

36. Two comments requested that FDA inform sponsors, as soon as possible, when the agency no longer believes that its (previously given) recommendations are adequate to obtain marketing approval and give the reason for its change of opinion along with the scientific rationale.

FDA does not have the resources to monitor all factors affecting continued validity of all guidance previously given. Therefore, FDA must place the burden on the sponsor periodically to seek confirmation that the recommendations it received from FDA still apply. This is not difficult if the sponsor is in frequent touch with FDA's review divisions and if the sponsor diligently reviews literature on relevant subjects. FDA will undertake to respond to specific inquiries by a sponsor concerning any change of FDA's position or previous advice.

37. Another comment suggested that FDA should, on request, provide recommendations concerning how to prove clinical superiority of a drug in order to show that it is "different" within the meaning of proposed § 316.3.

FDA advises that, if asked such a question, FDA will ordinarily recommend head-to-head clinical trails between the drugs, as this will normally be what is necessary to demonstrate clinical superiority to FDA's satisfaction. In addition, FDA may suggest endpoints for such studies.

38. Another comment requested that FDA develop a mechanism to notify sponsors early in the development process whether their drugs are the same as one being developed by another sponsor and whether either drug is considered a macromolecular drug or a micromolecular drug.

FDA advises that information on the existence of investigational products generally is confidential and may not be disclosed. In addition, FDA would normally not be able to determine whether drugs are the same or different until all data for marketing applications for both drugs are submitted. Hence, FDA declines to provide the requested early information and advice.

39. Another comment expressed concern that small firms are disadvantaged compared to multinational corporations with respect to their ability to learn about parallel research of another firm on the same drug. To investigate this possible bias against small firms, the comment proposed a full-scale economic assessment of this rule.

FDA does not agree that small firms are at a unique information disadvantage when developing orphan drugs. Imperfect knowledge about competitors' research is an expected risk factor in any research program, and, while small firms are inherently less able to tolerate excessive financial risk-taking, imperfect knowledge about competitor research is probably a less important risk factor for orphan drugs than for other pharmaceuticals. Orphan product development has been extensively publicized, both in the trade press and in sponsors' and investigators' efforts to locate test subjects, so that subsequent researchers in product areas where high research costs are likely almost always to have considerable information about competitors' efforts. Even if small firms had such a disadvantage, FDA cannot make confidential commercial information available. Therefore, FDA believes that a full-scale economic assessment of this aspect of the rule would be pointless.

40. Several comments suggested that FDA adopt time limits for response to requests for written recommendations as well as responses to requests on all matters associated with administration of the Orphan Drug Act.

Due to resource limitations, FDA cannot now impose time limits on itself for response to applications and requests pursuant to the Orphan Drug Act. However, the agency will respond to requests as expeditiously as its resources will allow.

41. One comment asked that the rule include the address for submitting requests for FDA action under this rule.

FDA agrees and has added the address of the Office of Orphan Products Development to the final rule in new § 316.4.

D. Designation of Orphan Drugs Based on Prevalence

42. Another comment recommended the removal of the requirement that a drug be designated as an orphan drug in order for the sponsor to be entitled to apply for orphan-product grants. The comment expressed a need for grants to support clinical studies on orphan devices and medical foods.

FDA advises that the Orphan Drug Amendments of 1988 (Pub. L. 100–290) provided that medical foods and medical devices for rare disease or conditions are eligible for grants and

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contracts to support clinical studies of safety and effectiveness. The preamble to the NPRM was in error to the extent that it implied the contrary. FDA solicits grant applications for clinical studies on medical devices and medical foods as well as on drugs and biologicals intended for rare diseases or conditions.

43. One comment suggested that there should be a process for designating medical foods and medical devices for rare diseases or conditions in light of the fact that the act now recognizes these and provides for grants and contracts to support clinical studies on these products.

FDA does not agree that a process for designating medical foods and medical devices for rare diseases or conditions is necessary. Although eligible for grants and contracts, sponsors of orphan medical devices and medical foods are not eligible for exclusive marketing rights. Hence, the main purpose for designation does not exist so far as these products are concerned. Further, with respect to grants and contracts, FDA's experience to date shows that a designation process would be unnecessary in order to establish eligibility for grants and contracts.

44. On its own initiative, FDA is adding to § 316.20(b)(4) a requirement that a description of the product for which orphan-drug designation is requested be submitted with the application for designation. This obviously important requirement clearly was within the scope of the NPRM and its omission was an oversight.

45. A comment requested that FDA make clear that the agency can grant orphan-drug designation to new versions of currently marketed orphan drugs if they are clinically superior to the original.

Orphan-drug designation can be granted to new sponsors of drugs currently protected by orphan-drug exclusive marketing if such sponsors provide a plausible scientific rationale in an application submitted pursuant to § 316.20 that studies to be conducted on the drug may result in a finding of clinical superiority over the marketed drug.

46. Another comment stated that authoritative information required to establish prevalence of a disease or condition and/or cost recovery estimates may not be available and the final rule should require only the best information available or all available references known to the sponsor.

FDA expects that applicants for orphan-drug designation will make every effort to survey the literature and obtain all information available on the prevalence of the indicated disease or condition and cost and marketing information, where required. Obviously, if information is not available, it cannot be submitted, but FDA expects sponsors to make a diligent search.

47. A comment expressed a fear that basing the prevalence criterion on the number of diagnosed patients who could benefit from the treatment makes possible orphan designation for a drug with a huge patient class.

FDA acknowledges that improved methods of diagnosis, better screening, or altered attitudes towards the need for therapy may produce a large increase in the number of patients who are diagnosed with a disease and could benefit from a drug. Prior to the development of such new diagnostic methods, better screening or new attitudes, however, FDA has no way of determining the likely treatment population other than by relying on current diagnostic methods and treatment attitudes.

48. A comment stated that it is unclear how FDA intends to handle investigational orphan drugs that are also being studied for common indications.

FDA advises that when a drug is being studied for a common as well as a rare disease, the rare disease indication will be handled just as it would be for a drug being studied only for a rare disease.

49. A comment requested that the agency provide substantive guidance, clarification, or definition on how an applicant can demonstrate that a subset of patients is "medically plausible."

FDA declines to provide examples of medical plausibility or to further develop the definition of this term. Application of the concept is a matter of judgment based on the specific facts of each case. Also, any hypothetical examples FDA might provide could well be misleading.

50. One comment argued that the proposed requirement that sponsors show the actual number of diagnosed cases in order to obtain orphan drug designation would be burdensome. For many diseases, the comment argued, there is little epidemilogical data giving the actual number of affected patients. It suggested that the appropriate number for determining prevalence of a disease is one which reflects both diagnosed and undiagnosed people.

FDA has already stated its strong preference for counting only diagnosed symptomatic patients in determining prevalence as the best approach to fulfill the purposes of the Orphan Drug Act. There is a lack of existing data and of precise methods for identifying the number of undiagnosed and asymptomatic patients who have a given disease. To impose such a requirement would add considerably to the cost of submitting requests for orphan drug designation without significant improvement of the factual bases for such requests.

51. Another comment agreed with the requirement that sponsors demonstrate that the actual number of diagnosed cases does not exceed 200,000 persons in the United States as of the date of application of designation. However, the comment requested that the agency go further and include the requirement in the final regulation itself rather than just in the preamble.

FDA agrees and is amending § 316.21(b) in the final rule accordingly.

52. Two comments argued that the requirement in proposed § 316.21(b)(2) that a sponsor show estimated prevalence of any other disease or condition for which the drug has been approved or is being developed is immaterial and burdensome.

The agency has reconsidered the proposed requirement and decided that such information would only be necessary in special circumstances, and will not be routinely required to make a decision on applications for designation. The regulation has been revised to require the information only upon request by FDA.

53. One comment suggested that FDA should divulge its sources and the processes whereby it verifies that the sponsor's prevalence data are correct.

FDA will on request provide a list of its sources used for verification of its conclusion as to the prevalence of a disease or condition. In the process, FDA will not provide any materials which it is obligated to treat as trade secret or confidential.

54. A comment suggested that in the case of vaccines, disease prevalence should be calculated based on an average annual target population over the prior 7 years rather than on the target population at the time of submission of the application for orphan designation. This, the comment argued, would provide greater predictability to the prospective sponsor of an orphan vaccine.

Under the terms of 21 U.S.C. 360bb, determinations "shall be made on the basis of the facts and circumstances as of the date such drug is designated * * *." FDA has interpreted this language to require that estimates of target population should reflect numbers of persons who would receive the vaccine as of the date of designation. The agency does not believe that the law contemplates the use of predictive models for growth or decline of disease populations.

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55. Another comment stated that, because data on the side effects of cancer or its treatment are limited or nonexistent, sponsors requesting designation of drugs for patients refractory to primary cancer therapies or other cancer subgroups should be able to rely on references to published incidence data, mortality tables, and expert medical testimony.

FDA advises that, where data are limited, sponsors should provide the best data available. Where published incidence data, mortality tables, and expert medical testimony are all that is available, this will normally be sufficient.

The comment further recommended that the final rule provide guidance including references to methods for deriving estimated prevalence data by using published incidence data.

FDA declines to provide such guidance as part of this published final rule but will provide data on methods of extrapolation when asked about this by potential sponsors regarding specific diseases.

56. One comment argued that FDA should provide for denial of designation if it is obvious that the drug will be used for nonorphan diseases or conditions with prevalence in excess of 200,000.

FDA will deny an orphan-drug designation application if it finds that the proposed orphan indication is a counterfeit, i.e., an artificial subset of the total population of potential users of the drug. However, the agency will continue to grant orphan drug designations for drugs that are being investigated for or are already approved for common diseases and conditions when there is also a rare disease for which the drug may be useful and is being studied, if the drug meets the orphan-drug criteria. The incentives of the Orphan Drug Act are needed to encourage testing and development of drugs for rare diseases or conditions even when a drug in question is being tested or approved for a more common indication. Otherwise, sponsors may be deterred by the lack of potential profit from testing drugs for rare diseases.

57. One comment suggested that § 316.26, which deals with amendments to orphan-drug designation, be broadened to allow such amendments when there are changes in medical technology or where diagnostic capabilities for a disease are improved.

FDA agrees that such changes are warranted, but only when the advances concerned are unanticipated. FDA has amended the final rule to this effect.

58. Several comments suggested that orphan-drug designation and exclusive marketing should be revoked when FDA determines that a drug that it has designated is later proved to have commercial potential or when the prevalence of the indicated rare disease or condition later exceeds 200,000 people in the United States.

FDA advises that legislation that would have authorized FDA to take such actions was vetoed by the President in 1990.

59. One comment argued that FDA had not sufficiently considered when and on what terms it will suspend (as distinguished from revoke) an orphan drug designation under § 316.29. The comment inquired as to when and under what terms FDA would restore a suspended designation.

After considering this comment, the agency concludes that it should not suspend an orphan drug designation on the grounds stated in § 316.29 but should only revoke it. The possibility of suspension raises troublesome questions about bases for and conditions of reinstatement of designation and the rights of subsequent sponsors. Hence, FDA has decided that, when the conditions set forth in § 316.29 occur (untrue statement of material fact, or omission of material information, or ineligibility of the drug at the time of designation), the appropriate remedy is permanent revocation of designation and suspension or withdrawal of exclusive marketing rights, with no eligibility for reinstatement of such rights. FDA has amended § 316.29 to reflect this conclusion.

E. Designation of Orphan Drugs Based on Nonrecovery of Cost

60. One comment concerning § 316.21 suggested a different approach for verifying data estimates and their justifications. The comment suggested that the sponsor be required to obtain an independent certified public accountant (CPA) report on certain agreed-upon procedures with respect to data, estimates and justification provided. Next, FDA, the sponsor, and the CPA would agree on procedures tailored to address matters of specific interest to the agency. Then, the independent CPA would report on the results of applying these procedures in a summary of findings—negative, assurance, or both. Lastly, the level of assurance provided in the independent CPA's report on how the agreed upon procedures would be applied would depend on the nature and scope of the procedures.

The comment suggested the following specific change in the text of § 316.21(c)(8):

(8) the sponsor shall submit a report of an independent Certified Public Accountant in accordance with Statement on Standards for Attestation established by the American Institute of Certified Public Accountants on agreed upon procedures performed with respect to the data, estimates, and justifications submitted pursuant to this section. Cost data shall be determined in accordance with generally accepted accounting principles.

FDA agrees that the suggested change is appropriate and has added the quoted passage to the final rule.

61. A comment stated that FDA has seriously underestimated the impact on multi-national corporations of demonstrating a lack of profitability in light of the fact that multi-national corporations will find it very difficult to collect information on the costs of orphan drug development and to separate those costs from costs of other research and development activities. According to the comment, the requirement of collection and separation will discourage use of orphan-drug incentives by multi-national corporations.

FDA believes that, although multi-national corporations may face problems that others do not, the potential benefits of orphan drug exclusive marketing would seem to outweigh the burden of separating costs between profitable ventures and orphan drug research and development projects.

62. Another comment correctly noted a typographical error in § 316.24(a): A reference to § 316.26, should have been a reference to § 316.25.

The error is being corrected in the final rule.

63. A comment suggested that orphan-drug designation should be denied for drugs that are likely to have commercial and competitive viability, even in small populations. The comment expressed concern that the exclusive marketing provisions of the act will limit the competition that has existed among manufacturers of blood clotting factor in the past. Alleging that this competition has kept prices down.

Existing provisions of the act do not provide a "commercial viability" basis for denial of requests for orphan drug designation when such drugs are for populations of 200,000 or less. Indeed, upon enacting an amendment to the Orphan Drug Act in 1984, Congress expressed its determination to accept the possibility that a designated orphan drug might be commercially viable with or without orphan drug exclusive marketing. (See 130 Congressional Record, S.14254 Floor Debates, October 11, 1984).

F. FDA Procedures

64. On its own initiative, FDA has added new § 316.30, requiring sponsors

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of designated orphan drugs to submit annual reports detailing progress made in the development of their orphan drugs in the past year. The agency believes that this provision is within the scope of the NPRM and will allow FDA to follow the development of orphan drugs and to identify and help to remove roadblocks to drug development and marketing.

65. A comment concerning § 316.27 argued that submission to FDA of copies of agreements embodying transfers of ownership of orphan-drug designation rights should be voluntary and not mandatory.

FDA agrees, and § 316.27(a)(2)(iii) has been changed in the final rule to make clear that either a list of rights assigned and reserved or copies of relevant agreements will meet the requirement of this paragraph.

66. Several comments argued that FDA should establish a process whereby the agency routinely informs sponsors when they are investigating drugs whose approval is likely to be barred by the Orphan Drug Act.

FDA believes that it is now adequately making this information available. The agency provides a list (updated monthly) of all designated orphan drugs to all sponsors who file a request for orphan-drug designation. Additionally, this list is available upon request from the National Information Center for Orphan Drugs and Rare Diseases (NICODARD), P.O. Box 1133, Washington, DC 20013–1133 (phone 1–800–456–3505). Hence, no new procedure is necessary.

66a. On its own initiative, FDA is revising proposed § 316.28 to reflect current practice of making available monthly an updated list of all designated orphan drugs and making available annually a cumulative updated list of all designated orphan drugs. In the past, the agency published an annual list in the **Federal Register**; however, it has found that its current practice is a more effective means of making the information available in a timely manner. The lists are on display at the FDA Dockets Management Branch and are available from NICODARD (see comment 66).

67. Several comments by holders of orphan-drug exclusive approval requested that such holders be accorded notice and an opportunity for a hearing when faced with the imminent approval of a similar drug that FDA considers to be a different drug for purposes of the act.

On March 4, 1987, in response to a citizen petition filed by Genentech, Inc., FDA declined to establish such a challenge procedure, citing the following grounds: (1) There is no property right to exclusive approval under the Orphan Drug Act; and (2) procedures are already in place that accord a holder of exclusive approval all the process that would be due under these circumstances. These procedures include the citizen petition procedure (21 CFR 10.30) and a right of subsequent judicial review in the courts.

In the NPRM (section II.I. (56 FR 3344)), FDA cited the following reasons for declining to create such procedures: (1) Neither the Constitution, nor the Administrative Procedure Act, nor the Orphan Drug Act requires a hearing of this kind; (2) hearings are time consuming and resource intensive; and (3) the citizen petition procedure is available to a holder of exclusive approval. Furthermore, in the NPRM, FDA refused to propose creation of a less formal nonhearing administrative challenge procedure because: (1) There is no requirement for it under the Constitution or any statute; (2) postdecisional judicial review is preferable to an administrative challenge procedure because a predecisional challenge procedure would be time consuming and could be used for purposes of delay; (3) it would be difficult to determine who should have the right to challenge an incipient approval and who would be entitled to what notice of what anticipated agency action; and, finally, (4) a predecisional administrative challenge procedure would present difficulty due to the nondisclosability of relevant information under FDA's public information regulations.

Despite a careful reconsideration of its position on the question of establishing predecisional challenge procedures, the agency declines to adopt such procedures. The other reasons given in the NPRM for declining to do so are still valid and even if a reviewing court were to hold that orphan drug exclusivity is a constitutionally protected property right, such a holding would not automatically require that a firm whose drug has been granted exclusivity be accorded a predecisional hearing. *Matthews* v. *Eldridge*, 424 U.S. 319 (1976); *Mackey* v. *Montrym*, 443 U.S. 1 (1979); *Barry* v. *Barchi*, 443 U.S. 1 (1979). Under these and other cases, the "property" right to exclusive marketing, if it exists, does not always require that a hearing take place before approval of what FDA concludes is a similar but different drug.

FDA is still persuaded that its current regulations satisfy any applicable requirement of due process. Insofar as notice is concerned, in FDA's view, a holder of exclusive approval would learn that a potential competitor drug has been designated, as FDA is required to publish all such designations. See 21 U.S.C. 360bb(c) and § 316.52(d), the latter of which is codified by this notice. As to a procedure for challenging an approval, either impending or after the fact, the citizen petition procedure provides such a procedure, and the holder of the earlier designation has a right to seek judicial review of an adverse decision. This procedure is sufficient under *Barry* v. *Barchi, supra*.

In addition, FDA is still concerned about the potential for holders of exclusive approval to delay the marketing of competitors' approvable subsequent drugs by use of any challenge procedure. The fact that all challenge procedures, particularly hearings, are time consuming and expensive, adds to FDA's reluctance to create such procedures.

For the above reasons, FDA has, after careful consideration, decided that the final rule should not include an opportunity for a hearing or other challenge procedures for holders of exclusive approval to challenge subsequent drug approvals.

68. One comment argued that FDA should notify sponsors of marketing applications for orphan drugs when another sponsor of the same drug for the same use has attained orphan drug exclusive marketing status. The comment suggested that the sponsor barred from marketing approval by orphan drug exclusive marketing should be informed, within 30 days, of the approval of the drug receiving exclusive approval.

FDA disagrees. As stated previously, FDA usually does not know that approval of a marketing application is barred by the Orphan Drug Act until the review of that application shows that the subsequent drug is the same as the pioneer. Hence, FDA cannot set a time limit on notification of subsequent sponsors. In addition, FDA routinely publicizes all marketing application approvals. Therefore, it is reasonable to expect that subsequent sponsors can, with minimal effort, learn of these approvals.

G. Orphan-Drug Exclusive Approval

69. A comment suggested that § 316.30 be reworded to allow more than one company to share exclusive marketing rights if the first company to obtain FDA approval agrees.

FDA advises that § 316.30(a)(3) provides that a holder of exclusive approval may give consent for other marketing applications to gain approval. This provision enables the holder to share exclusive marketing rights with

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any number of other sponsors. The agency believes that the current wording of this paragraph need not be changed in order to achieve the objective of the comment.

70. A comment requested that the high cost of an orphan drug be considered evidence that "sufficient quantities" of the drug are not available "to meet the needs of persons with the disease or condition for which the drug was designated." Such a finding would then allow for the approval of subsequent identical drugs.

FDA does not have the authority under existing law to equate high cost with lack of sufficient quantities, even though cost may affect access to a drug. As Congress used the term, "sufficient quantities" refers only the presence of enough drug and the means of its administration to meet the needs of all in the United States with the disease or condition for which the drug was designated.

71. Two comments urged that § 316.36 clearly set forth the criteria and procedure for a determination of whether "sufficient quantities" are available. One comment suggested that the lack of sufficient quantities must be "long-term" or "deliberate." Alternatively, the comment suggested that a finding of a lack of commitment on the part of the exclusive marketing holder should be necessary to break exclusive marketing. A third comment suggested as a standard for agency action the inability to provide the drug for 1 year. Two comments requested that FDA make allowances for temporary production difficulties, disruptions caused by natural disasters, interruptions in supplies and component parts, economic crises, or other causes beyond the holder's control. One comment suggested that the sponsor should be given adequate time to restore supplies and that the revocation should not occur unless another sponsor can supply at least 75 percent of the market at least 12 months earlier than the first-approved sponsor. This comment urged a right of appeal by the pioneer.

FDA advises that it will act quickly to approve another marketing application when there are insufficient supplies of the drug or insufficient means of its administration for any reason. In granting FDA authority to revoke exclusive marketing because of insufficient quantities, Congress did not refer in any way to the behavior or attitude of the initial holder, and revocation is in no sense a punishment. The provision exists solely in order to get drugs quickly to the people who need them. Accordingly, in determining whether there are "sufficient quantities" of a drug, FDA will always make the needs of patients its primary concern. For the same reason, the agency declines to create an administrative appeals process for reviewing decisions under § 316.36.

72. Another comment proposed that FDA impose, as a condition of maintaining exclusive marketing rights, a requirement that holders of such rights must sell whatever quantities are necessary to subsequent sponsors in order to conduct required comparative studies. If the holder refused, it would be given 60 days to comply or lose exclusive marketing rights.

FDA believes that most subsequent sponsors will have access to the holder's product. However, if that is not the case, FDA would be without authority to impose the condition described. Congress has set forth only two situations in which exclusive marketing rights can be removed. The situation described above is not one of them.

73. Another comment, which agreed with FDA's decision to rule out cost considerations in determining the existence of sufficient quantities of orphan drugs, suggested that the agency amend the final rule to specify that no authority to do so exists.

FDA believes that statements in the preambles to the NPRM and to this final rule are sufficient notification that the agency believes it lacks authority to consider costs of drugs in rendering decisions under § 316.36. Hence, no change in the rule is necessary.

H. Open Protocols

74. One comment argued that FDA should make clear that the final rule will require parallel controlled studies in order to obtain marketing approval. The comment noted that open protocols may be a threat to encouraging placebo-controlled studies for marketing approval.

FDA understands that the existence of open protocols may increase the difficulty of recruiting subjects for placebo-controlled studies. However, Congress has mandated that FDA encourage open protocols, and this final rule will do so. This does not mean that FDA is relaxing its standards for the approval of drugs. The requirements for demonstrating safety and effectiveness are not any less for orphan drugs than for any other drugs.

I. Availability of Information

75. One comment suggested that § 316.52 should be amended to provide that notice in the **Federal Register** be published concurrently with each orphan-drug designation decision.

FDA disagrees with this suggestion. A current list of drugs designated as orphan drugs is freely available from NICODARD (see comment 66 for address and telephone number). Publishing each orphan-drug designation in the **Federal Register** would be an unduly burdensome task.

76. A comment suggested that as much information as possible regarding details about designated orphan drugs and applications for designation should be made available because of the public's "right to know."

FDA advises that the agency releases as much information as it can consistent with the Freedom of Information Act, FDA's regulations, and long-standing policies concerning the protection of trade secret data and confidential commercial information.

77. Two comments suggested that FDA inform a holder of exclusive marketing rights when a subsequent sponsor has applied for designation for the same drug for the same indication and that a decision concerning the sameness or difference of the products should be made prior to the decision to designate the second drug.

FDA disagrees. As previously stated, current information on all designated orphan drugs is available from NICODARD (see comment 66). FDA is treating the filing of applications for designation as a submission of confidential information which will not be disclosed until and unless designation is granted. In addition, for reasons stated previously, FDA cannot make preliminary decisions as to the sameness or difference of any two drugs. Also, as stated in the NPRM preamble, FDA will designate a structurally identical subsequent drug as an orphan drug, even in the face of a holder's exclusive marketing rights, if the subsequent sponsor advances a plausible basis on which to conclude that its product may be proven "clinically superior." This is because FDA does not want to stifle research and development of potentially better drugs.

78. One comment stated that the impact of the regulation would be "major" for purposes of Executive Order 12291, which requires extensive regulatory impact and flexibility analyses prior to promulgation of regulations having a "major" impact on small businesses. The comment added an opinion that such an analysis would demonstrate that the agency's "original test" (the comment's meaning for this term is unclear) for determining sameness/difference presented a more cost-effective alternative without the adverse effect on competition, unlike the proposed policy.

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FDA disagrees with the premise that analyses under Executive Order 12291 are the appropriate means for evaluating the relative usefulness of methods for determining sameness/differences. FDA has consulted with the IOM in developing the adopted approach and will evaluate and propose revisions to the approach if necessary in the interests and needs of people with rare diseases and conditions.

79. One comment stated that FDA should be required to prepare an economic impact statement under the Regulatory Flexibility Act on grounds that the proposed rule adversely affects a significant number of small entities.

FDA disagrees because the overall impact of the Orphan Drug Act benefits small businesses, many of which would otherwise be unable to bear the substantial cost of new product development. Moreover, the economic effects of the proposed rule, and the final rule, are simply those contemplated by Congress in its enactment of the Orphan Drug Act. (See the discussion below in section III.)

III. Economic Impact

The agency has examined the economic impact of the final rule in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96–354) and concludes that this 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.

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. In debating the need for orphan drug exclusive marketing, Congress weighed the potential dangers of granting orphan drug exclusive marketing, which would limit competition, against the benefits to be gained by encouraging sponsors to develop drugs of marginal commercial value. In passing the law, Congress determined that the benefits exceeded the dangers. Any form of exclusive marketing may have negative consequences, such as noncompetitive pricing. To date, however, there has been insufficient experience with the implementation of the statute to judge whether an optimal benefit-cost balance has been attained. It is clear, nonetheless, that these incentives have been highly successful in contributing to the development and approval of orphan drugs that would not otherwise have been developed. Thus, in FDA's view, the essential benefit-cost considerations of Executive Order 12291 have been satisfied in favor of the rule as here published.

The agency also recognizes that changes in the statutory incentive structure would theoretically produce corresponding changes in the level of benefits, i.e., the number of orphan drugs developed. FDA, however, concludes that further incremental analysis of the statutory provisions would be highly conjectural and beyond the availability of meaningful data from experience to date.

The Regulatory Flexibility Act requires that the agency consider the impact of the regulation on small entities. FDA believes that these rules benefit, rather than disadvantage, most affected small businesses. Prior to enactment of the Orphan Drug Act, few small businesses could afford to devote resources to the discovery of new treatments for rate diseases, because the small market for such products severely limited the profitability of this research. Subsequent to enactment, the combined stimulus of research grants, tax credits, and exclusive marketing influenced many small firms to develop new products for formerly inaccessible markets. FDA finds therefore that, in general, the incentives provided under the act will serve to enhance the viability and competitiveness of small entities.

IV. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Paperwork Reduction Act of 1980

This final 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 information collections will not be effective until OMB approval is obtained. The title, description, and identification of those who will respond to the information collection requirements 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.

Description: These final regulations specify the procedures for sponsors of orphan drugs to use in availing themselves of the incentive 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 hours per response	Annual burden hours
316.2 and 316.10 ..	3	1	125	375
316.20	90	1.78	125	20,025
316.22	5	1	2	10
316.27	5	1	4	20
316.30	450	1	2	900
316.36	0.2	3	15	9
Total .	.....	.....	.....	21,339

List of Subjects in 21 CFR Part 316

Administrative practice and procedures, drugs, Orphan drugs, Reporting and recordkeeping requirement.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 316 is added as follows:

PART 316—ORPHAN DRUGS

Subpart A—General Provisions

Sec.

316.1 Scope of this part.
316.2 Purpose.
316.3 Definitions.
316.4 Address for submissions.

Subpart B—Written Recommendations for Investigations of Orphan Drugs

316.10 Content and format of a request for written recommendations.
316.12 Providing written recommendations.
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Subpart C—Designation of an Orphan Drug

316.20 Content and format of a request for orphan-drug designation.
316.21 Verification of orphan-drug status.
316.22 Permanent-resident agent for foreign sponsor.

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316.23 Timing of requests for orphan-drug designation; designation of already approved drugs.
316.24 Granting orphan-drug designation.
316.25 Refusal to grant orphan-drug designation.
316.26 Amendment to orphan-drug designation.
316.27 Change in ownership of orphan-drug designation.
316.28 Publication of orphan-drug designations.
316.29 Revocation of orphan-drug designation.
316.30 Annual reports of holder of orphan-drug designation.

Subpart D—Orphan-drug Exclusive Approval

316.31 Scope of orphan-drug exclusive approval.
316.34 FDA recognition of exclusive approval.
316.36 Insufficient quantities of orphan drugs.

Subpart E—Open Protocols for Investigations

316.40 Treatment use of a designated orphan drug.

Subpart F—Availability of Information

316.50 Guidelines.
316.52 Availability for public disclosure of data and information in requests and applications.

Authority: Secs. 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.

(c) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

§ 316.2 Purpose.

The purpose of this part is to establish standards and procedures for determining eligibility for the benefits provided for in section 2 of the Orphan Drug Act, including written recommendations for investigations of orphan drugs, a 7-year period of exclusive marketing, and treatment use of investigational orphan drugs. This part is also intended to satisfy Congress' requirements that FDA promulgate procedures for the implementation of sections 525(a) and 526(a) of the act.

§ 316.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms apply to this part:

(1) *Act* means the Federal Food, Drug, and Cosmetic Act as amended by section 2 of the Orphan Drug Act (sections 525–528 (21 U.S.C. 360aa–360dd)).

(2) *Active moiety* means the 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.

(3) *Clinically superior* means that a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved orphan drug (that is otherwise the same drug) in one or more of the following ways:

(i) Greater effectiveness than an 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

(ii) Greater safety in a substantial portion of the target populations, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. In some cases, direct comparative clinical trials will be necessary; or

(iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.

(4) *Director* means the Director of FDA's Office of Orphan Products Development.

(5) *FDA* means the Food and Drug Administration.

(6) *Holder* means the sponsor in whose name an orphan drug is designated and approved.

(7) *IND* means an investigational new drug application under part 312 of this chapter.

(8) *Manufacturer* means any person or agency engaged in the manufacture of a drug that is subject to investigation and approval under the act or the biologics provisions of the Public Health Service Act (42 U.S.C. 262–263).

(9) *Marketing application* means an application for approval of a new drug filed under section 505(b) of the act, a request for certification of an antibiotic under section 507 of the act, or an application for a biological product/establishment license submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

(10) *Orphan drug* means a drug intended for use in a rare disease or condition as defined in section 526 of the act.

(11) *Orphan-drug designation* means FDA's act of granting a request for designation under section 526 of the act.

(12) *Orphan-drug exclusive approval* or *exclusive approval* means that, effective on the date of FDA approval as stated in the approval letter of a marketing application for a sponsor of a designated orphan drug, no approval will be given to a subsequent sponsor of the same drug product for the same indication for 7 years, except as otherwise provided by law or in this part.

(13) *Same drug* means:

(i) If it is a drug composed of small molecules, a drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative such as a complex, chelate or clathrate has not been previously approved, except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.

(ii) If it is a drug composed of large molecules (macromolecules), a drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use as a previously approved drug, except that, if the subsequent drug can be shown to be clinically superior, it will not be considered to be the same drug. This criterion will be applied as follows to different kinds of macromolecules:

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(A) Two protein drugs would be considered the same if the only differences in structure between them were due to post-translational events or infidelity of translation or transcription or were 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 differences 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 postpolymerization 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, deoxyribose, 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, would be considered the same unless the subsequent drug was shown to be clinically superior.

(14) *Sponsor* means the entity that assumes responsibility for a clinical or nonclinical investigation of a drug, including the responsibility for compliance with applicable provisions of the act and regulations. A sponsor may be an individual, partnership, corporation, or Government agency and may be a manufacturer, scientific institution, or an investigator regularly and lawfully engaged in the investigation of drugs. For purposes of the Orphan Drug Act, FDA considers the real party or parties in interest to be a sponsor.

§ 316.4 Address for submissions.

All correspondence and requests for FDA action pursuant to the provisions of this rule should be addressed as follows: Office of Orphan Products Development (HF-35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Subpart B—Written Recommendations for Investigations of Orphan Drugs

§ 316.10 Content and format of a request for written recommendations.

(a) A sponsor's request for written recommendations from FDA concerning the nonclinical and clinical investigations necessary for approval of a marketing application shall be submitted in the form and contain the information required in this section. FDA may require the sponsor to submit information in addition to that specified in paragraph (b) of this section if FDA determines that the sponsor's initial request does not contain adequate information on which to base recommendations.

(b) A sponsor shall submit two copies of a completed, dated, and signed request for written recommendations that contains the following:

(1) The sponsor's name and address.

(2) A statement that the sponsor is requesting written recommendations on orphan-drug development under section 525 of the act.

(3) The name of the sponsor's primary contact person and/or resident agent, and the person's title, address, and telephone number.

(4) The generic name and trade name, if any, of the drug and a list of the drug product's components or description of the drug product's formulation, and chemical and physical properties.

(5) The proposed dosage form and route of administration.

(6) A description of the disease or condition for which the drug is proposed to be investigated and the proposed indication or indications for use for such disease or condition.

(7) Current regulatory and marketing status and history of the drug product, including:

(i) Whether the product is the subject of an IND or a marketing application (if the product is the subject of an IND or a marketing application, the IND or marketing application numbers should be stated and the investigational or approved indication or indications for use specified);

(ii) Known marketing experience or investigational status outside the United States;

(iii) So far as is known or can be determined, all indications previously or currently under investigation anywhere;

(iv) All adverse regulatory actions taken by the United States or foreign authorities.

(8) The basis for concluding that the drug is for a disease or condition that is rare in the United States, including the following:

(i) The size and other known demographic characteristics of the patient population affected and the source of this information.

(ii) For drugs intended for diseases or conditions affecting 200,000 or more people in the United States, or for a vaccine, diagnostic drug, or preventive drug that would be given to 200,000 or more persons per year, a summary of the sponsor's basis for believing that the disease or condition described in paragraph (b)(6) of this section occurs so infrequently that there is no reasonable expectation that the costs of drug development and marketing will be recovered in future sales of the drug in the United States. The estimated costs and sales data should be submitted as provided for in § 316.21(c).

(9) A summary and analysis of available data on the pharmacologic effects of the drug.

(10) A summary and analysis of available nonclinical and clinical data pertinent to the drug and the disease to be studied including copies of pertinent published reports. When a drug proposed for orphan drug designation is intended to treat a lift-threatening or severely debilitating illness, especially where no satisfactory alternative therapy exists, the sponsor may wish voluntarily to provide this information. A sponsor of such a drug may be entitled to expeditious development, evaluation, and marketing under 21 CFR part 312, subpart E.

(11) An explanation of how the data summarized and analyzed under paragraphs (b)(9) and (b)(10) of this section support the rationale for use of the drug in the rare disease or condition.

(12) A definition of the population from which subjects will be identified for clinical trials, if known.

(13) A detailed outline of any protocols under which the drug has been or is being studied for the rare disease or condition and a summary and analysis of any available data from such studies.

(14) The sponsor's proposal as to the scope of nonclinical and clinical investigations needed to establish the safety and effectiveness of the drug.

(15) Detailed protocols for each proposed United States or foreign clinical investigation, if available.

(16) Specific questions to be addressed by FDA in its recommendations for nonclinical laboratory studies and clinical investigations.

§ 316.12 Providing written recommendations.

(a) FDA will provide the sponsor with written recommendations concerning the nonclinical laboratory studies and clinical investigations necessary for approval of a marketing application if none of the reasons described in § 316.14 for refusing to do so applies.

(b) When a sponsor seeks written recommendations at a stage of drug

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development at which advice on any clinical investigations, or on particular investigations would be premature, FDA's response may be limited to written recommendations concerning only nonclinical laboratory studies, or only certain of the clinical studies (e.g., Phase 1 studies as described in § 312.21 of this chapter). Prior to providing written recommendations for the clinical investigations required to achieve marketing approval, FDA may require that the results of the nonclinical laboratory studies or completed early clinical studies be submitted to FDA for agency review.

§ 316.14 Refusal to provide written recommendations.

(a) FDA may refuse to provide written recommendations concerning the nonclinical laboratory studies and clinical investigations necessary for approval of a marketing application for any of the following reasons:

(1) The information required to be submitted by § 316.10(b) has not been submitted, or the information submitted is incomplete.

(2) There is insufficient information about:

(i) The drug to identify the active moiety and its physical and chemical properties, if these characteristics can be determined; or

(ii) The disease or condition to determine that the disease or condition is rare in the United States; or

(iii) The reasons for believing that the drug may be useful for treating the rare disease or condition with that drug; or

(iv) The regulatory and marketing history of the drug to determine the scope and type of investigations that have already been conducted on the drug for the rare disease or condition; or

(v) The plan of study for establishing the safety and effectiveness of the drug for treatment of the rare disease or condition.

(3) The specific questions for which the sponsor seeks the advice of the agency are unclear or are not sufficiently specific.

(4) On the basis of the information submitted and on other information available to the agency, FDA determines that the disease or condition for which the drug is intended is not rare in the United States.

(5) On the basis of the information submitted and on other information available to the agency, FDA determines that there is an inadequate basis for permitting investigational use of the drug under part 312 of this chapter for the rare disease or condition.

(6) The request for information contains an untrue statement of material fact.

(b) A refusal to provide written recommendations will be in writing and will include a statement of the reason for FDA's refusal. Where practicable, FDA will describe the information or material it requires or the conditions the sponsor must meet for FDA to provide recommendations.

(c) Within 90 days after the date of a letter from FDA requesting additional information or material or setting forth the conditions that the sponsor is asked to meet, the sponsor shall either:

(1) Provide the information or material or amend the request for written recommendations to meet the conditions sought by FDA; or

(2) Withdraw the request for written recommendations. FDA will consider a sponsor's failure to respond within 90 days to an FDA letter requesting information or material or setting forth conditions to be met to be a withdrawal of the request for written recommendations.

Subpart C—Designation of an Orphan Drug

§ 316.20 Content and format of a request for orphan-drug designation.

(a) A sponsor that submits a request for orphan-drug designation of a drug for a specified rare disease or condition shall submit each request in the form and containing the information required in paragraph (b) of this section. A sponsor may request orphan-drug designation of a previously unapproved drug, or of a new orphan indication for an already marketed drug. In addition, a sponsor of a drug that is otherwise the same drug as an already approved orphan drug may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug. More than one sponsor may receive orphan-drug designation of the same drug for the same rare disease or condition, but each sponsor seeking orphan-drug designation must file a complete request for designation as provided in paragraph (b) of this section.

(b) A sponsor shall submit two copies of a completed, dated, and signed request for designation that contains the following:

(1) A statement that the sponsor requests orphan-drug designation for a rare disease or condition, which shall be identified with specificity.

(2) The name and address of the sponsor; the name of the sponsor's primary contact person and/or resident agent including title, address, and telephone number; the generic and trade name, if any, of the drug or drug product; and the name and address of the source of the drug if it is not manufactured by the sponsor.

(3) A description of the rare disease or condition for which the drug is being or will be investigated, the proposed indication or indications for use of the drug, and the reasons why such therapy is needed.

(4) A description of the drug and a discussion of the scientific rationale for the use of the drug for the rare disease or condition, including all data from nonclinical laboratory studies, clinical investigations, and other relevant data that are available to the sponsor, whether positive, negative, or inconclusive. Copies of pertinent unpublished and published papers are also required.

(5) Where the sponsor of a drug that is otherwise the same drug as an already-approved orphan drug seeks orphan-drug designation for the subsequent drug for the same rare disease or condition, an explanation of why the proposed variation may be clinically superior to the first drug.

(6) Where a drug is under development for only a subset of persons with a particular disease or condition, a demonstration that the subset is medically plausible.

(7) A summary of the regulatory status and marketing history of the drug in the United States and in foreign countries, e.g., IND and marketing application status and dispositions, what uses are under investigation and in what countries; for what indication is the drug approved in foreign countries; what adverse regulatory actions have been taken against the drug in any country.

(8) Documentation, with appended authoritative references, to demonstrate that:

(i) The disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year as specified in § 316.21(b), or

(ii) For a drug intended for diseases or conditions affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 200,000 or more persons per year in the United States, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States as specified in § 316.21(c).

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(9) A statement as to whether the sponsor submitting the request is the real party in interest of the development and the intended or actual production and sales of the product.

(c) Any of the information previously provided by the sponsor to FDA under Subpart B of this part may be referenced by specific page or location if it duplicates information required elsewhere in this section.

§ 316.21 Verification of orphan-drug status.

(a) So that FDA can determine whether a drug qualifies for orphan-drug designation under section 526(a) of the act, the sponsor shall include in its request to FDA for orphan-drug designation under § 316.20 either:

(1) Documentation as described in paragraph (b) of this section that the number of people affected by the disease or condition for which the drug product is indicated is fewer than 200,000 persons; or

(2) Documentation as described in paragraph (c) of this section that demonstrates that there is no reasonable expectation that the sales of the drug will be sufficient to offset the costs of developing the drug for the U.S. market and the costs of making the drug available in the United States.

(b) For the purpose of documenting that the number of people affected by the disease or condition for which the drug product is indicated is less than 200,000 persons, "prevalence" is defined as the number of persons in the United States who have been diagnosed as having the disease or condition at the time of the submission of the request for orphan-drug designation. To document the number of persons in the United States who have the disease or condition for which the drug is to be indicated, the sponsor shall submit to FDA evidence showing:

(1) The estimated prevalence of the disease or condition for which the drug is being developed, together with a list of the sources (including dates of information provided and literature citations) for the estimate;

(2) Upon request by FDA, the estimated prevalence of any other disease or condition for which the drug has already been approved or for which the drug is currently being developed, together with an explanation of the bases of these estimates; and

(3) The estimated number of people to whom the drug will be administered annually if the drug is a vaccine or is a drug intended for diagnosis or prevention of a rare disease or condition, together with an explanation of the bases of these estimates (including dates of information provided and literature citations).

(c) When submitting documentation that there is no reasonable expectation that costs of research and development of the drug for the disease or condition can be recovered by sales of the drug in the United States, the sponsor shall submit to FDA:

(1) Data on all costs that the sponsor has incurred in the course of developing the drug for the U.S. market. These costs shall include, but are not limited to, nonclinical laboratory studies, clinical studies, dosage form development, record and report maintenance, meetings with FDA, determination of patentability, preparation of designation request, IND/marketing application preparation, distribution of the drug under a "treatment" protocol, licensing costs, liability insurance, and overhead and depreciation. Furthermore, the sponsor shall demonstrate the reasonableness of the cost data. For example, if the sponsor has incurred costs for clinical investigations, the sponsor shall provide information on the number of investigations, the years in which they took place, and on the scope, duration, and number of patients that were involved in each investigation.

(2) If the drug was developed wholly or in part outside the United States, in addition to the documentation listed in paragraph (c)(1) of this section:

(i) Data on and justification for all costs that the sponsor has incurred outside of the United States in the course of developing the drug for the U.S. market. The justification, in addition to demonstrating the reasonableness of the cost data, must also explain the method that was used to determine which portion of the foreign development costs should be applied to the U.S. market, and what percent these costs are of total worldwide development costs. Any data submitted to foreign government authorities to support drug pricing determinations must be included with this information.

(ii) Data that show which foreign development costs were recovered through cost recovery procedures that are allowed during drug development in some foreign countries. For example, if the sponsor charged patients for the drug during clinical investigations, the revenues collected by the sponsor must be reported to FDA.

(3) In cases where the drug has already been approved for marketing for any indication or in cases where the drug is currently under investigation for one or more other indications (in addition to the indication for which orphan-drug designation is being sought), a clear explanation of and justification for the method that is used to apportion the development costs among the various indications.

(4) A statement of and justification for any development costs that the sponsor expects to incur after the submission of the designation request. In cases where the extent of these future development costs are not clear, the sponsor should request FDA's advice and assistance in estimating the scope of nonclinical laboratory studies and clinical investigations and other data that are needed to support marketing approval. Based on these recommendations, a cost estimate should be prepared.

(5) A statement of and justification for production and marketing costs that the sponsor has incurred in the past and expects to incur during the first 7 years that the drug is marketed.

(6) An estimate of and justification for the expected revenues from sales of the drug in the United States during its first 7 years of marketing. The justification should assume that the total market for the drug is equal to the prevalence of the disease or condition that the drug will be used to treat. The justification should include:

(i) An estimate of the expected market share of the drug in each of the first 7 years that it is marketed, together with an explanation of the basis for that estimate;

(ii) A projection of and justification for the price at which the drug will be sold; and

(iii) Comparisons with sales of similarly situated drugs, where available.

(7) The name of each country where the drug has already been approved for marketing for any indication, the dates of approval, the indication for which the drug is approved, and the annual sales and number of prescriptions in each country since the first approval date.

(8) A report of an independent certified public accountant in accordance with Statement on Standards for Attestation established by the American Institute of Certified Public Accountants on agreed upon procedures performed with respect to the data estimates and justifications submitted pursuant to this section. Cost data shall be determined in accordance with generally accepted accounting principles.

(d) A sponsor that is requesting orphan-drug designation for a drug designed to treat a disease or condition that affects 200,000 or more persons shall, at FDA's request, allow FDA or FDA-designated personnel to examine at reasonable times and in a reasonable

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manner all relevant financial records and sales data of the sponsor and manufacturer.

§ 316.22 Permanent-resident agent for foreign sponsor.

Every foreign sponsor that seeks orphan-drug designation shall name a permanent resident of the United States as the sponsor's agent upon whom service of all processes, notices, orders, decisions, requirements, and other communications may be made on behalf of the sponsor. Notifications of changes in such agents or changes of address of agents should preferably be provided in advance, but not later than 60 days after the effective date of such changes. The permanent-resident agent may be an individual, firm, or domestic corporation and may represent any number of sponsors. The name of the permanent-resident agent shall be provided to: Office of Orphan Products Development (HF–35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

§ 316.23 Timing of requests for orphan-drug designation; designation of already approved drugs.

(a) A sponsor may request orphan-drug designation at any time in the drug development process prior to the submission of a marketing application for the drug product for the orphan indication.

(b) A sponsor may request orphan-drug designation of an already approved drug product for an unapproved use without regard to whether the prior marketing approval was for an orphan-drug indication.

§ 316.24 Granting orphan-drug designation.

(a) FDA will grant the request for orphan-drug designation if none of the reasons described in § 316.25 for requiring or permitting refusal to grant such a request applies.

(b) When a request for orphan-drug designation is granted, FDA will notify the sponsor in writing and will publicize the orphan-drug designation in accordance with § 316.28.

§ 316.25 Refusal to grant orphan-drug designation.

(a) FDA will refuse to grant a request for orphan-drug designation if any of the following reasons apply:

(1) The drug is not intended for a rare disease or condition because:

(i) There is insufficient evidence to support the estimate that the drug is intended for treatment of a disease or condition in fewer than 200,000 people in the United States, or that the drug is intended for use in prevention or in diagnosis in fewer than 200,000 people annually in the United States; or

(ii) Where the drug is intended for prevention, diagnosis, or treatment of a disease or condition affecting 200,000 or more people in the United States, the sponsor has failed to demonstrate that there is no reasonable expectation that development and production costs will be recovered from sales of the drug for the orphan indication in the United States. A sponsor's failure to comply with § 316.21 shall constitute a failure to make the demonstration required in this paragraph.

(2) There is insufficient information about the drug, or the disease or condition for which it is intended, to establish a medically plausible basis for expecting the drug to be effective in the prevention, diagnosis, or treatment of that disease or condition.

(3) A drug that is otherwise the same drug as one that already has orphan-drug exclusive approval for the same rare disease or condition and the sponsor has not submitted a medically plausible hypothesis for the possible clinical superiority of the subsequent drug.

(b) FDA may refuse to grant a request for orphan-drug designation if the request for designation contains an untrue statement of material fact or omits material information.

§ 316.26 Amendment to orphan-drug designation.

(a) At any time prior to approval of a marketing application for a designated orphan drug, the sponsor holding designation may apply for an amendment to the indication stated in the orphan-drug designation if the proposed change is due to new and unexpected findings in research on the drugs, information arising from FDA recommendations, or unforeseen developments in treatment or diagnosis of the disease or condition.

(b) FDA will grant the amendment if it finds that the initial designation request was made in good faith and that the amendment is intended to conform the orphan-drug designation indication to the results of unanticipated research findings, to unforeseen developments in the treatment or diagnosis of the disease or condition, or to changes based on FDA recommendations, and that, as of the date of the submission of the amendment request, the amendment would not result in exceeding the prevalence or cost recovery thresholds in § 316.21 (a)(1) or (a)(2) upon which the drug was originally designated.

§ 316.27 Change in ownership of orphan-drug designation.

(a) A sponsor may transfer ownership of or any beneficial interest in the orphan-drug designation of a drug to a new sponsor. At the time of the transfer, the new and former owners are required to submit the following information to FDA:

(1) The former owner or assignor of rights shall submit a letter or other document that states that all or some rights to the orphan-drug designation of the drug have been transferred to the new owner or assignee and that a complete copy of the request for orphan-drug designation, including any amendments to the request, supplements to the granted request, and correspondence relevant to the orphan-drug designation, has been provided to the new owner or assignee.

(2) The new owner or assignee of rights shall submit a statement accepting orphan-drug designation and a letter or other document containing the following:

(i) The date that the change in ownership or assignment of rights is effective;

(ii) A statement that the new owner has a compete copy of the request for orphan-drug designation including any amendments to the request, supplements to the granted request, and correspondence relevant to the orphan-drug designation; and

(iii) A specific description of the rights that have been assigned and those that have been reserved. This may be satisfied by the submission of either a list of rights assigned and reserved or copies of all relevant agreements between assignors and assignees; and

(iv) The name and address of a new primary contact person or resident agent.

(b) No sponsor may relieve itself of responsibilities under the Orphan Drug Act or under this part by assigning rights to another person without:

(1) Assuring that the sponsor or the assignee will carry out such responsibilities; or

(2) Obtaining prior permission from FDA.

§ 316.28 Publication of orphan-drug designations.

Each month FDA will update a publically available list of drugs designated as orphan drugs. A cumulative, updated list of all designated drugs will be provided annually. These will be placed on file at the FDA Dockets Management Branch, and will contain the following information:

(a) The name and address of the manufacturer and sponsor;

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(b) The generic name and trade name, if any, of the drug and the date of the granting of orphan-drug designation;

(c) The rare disease or condition for which orphan-drug designation was granted; and

(d) The proposed indication for use of the drug.

§ 316.29 Revocation of orphan-drug designation.

(a) FDA may revoke orphan-drug designation for any drug if the agency finds that:

(1) The request for designation contained an untrue statement of material fact; or

(2) The request for designation omitted material information required by this part; or

(3) FDA subsequently finds that the drug in fact had not been eligible for orphan-drug designation at the time of submission of the request therefor.

(b) For an approved drug, revocation of orphan-drug designation also suspends or withdraws the sponsor's exclusive marketing rights for the drug but not the approval of the drug's marketing application.

(c) Where a drug has been designated as an orphan drug because the prevalence of a disease or condition (or, in the case of vaccines, diagnostic drugs, or preventive drugs, the target population) is under 200,000 in the United States at the time of designation, its designation will not be revoked on the ground that the prevalence of the disease or condition (or the target population) becomes more than 200,000 persons.

§ 316.30 Annual reports of holder of orphan-drug designation.

Within 14 months after the date on which a drug was designated as an orphan drug and annually thereafter until marketing approval, the sponsor of a designated drug shall submit a brief progress report to the FDA Office of Orphan Products Development on the drug that includes:

(a) A short account of the progress of drug development including a review of preclinical and clinical studies initiated, ongoing, and completed and a short summary of the status or results of such studies.

(b) A description of the investigational plan for the coming year, as well as any anticipated difficulties in development, testing, and marketing; and

(c) A brief discussion of any changes that may affect the orphan-drug status of the product. For example, for products nearing the end of the approval process, sponsors should discuss any disparity between the probable marketing indication and the designated indication as related to the need for an amendment to the orphan-drug designation pursuant to § 316.26.

Subpart D—Orphan-drug Exclusive Approval

§ 316.31 Scope of orphan-drug exclusive approval.

(a) After approval of a sponsor's marketing application for a designated orphan-drug product for treatment of the rare disease or condition concerning which orphan-drug designation was granted, FDA will not approve another sponsor's marketing application for the same drug before the expiration of 7 years from the date of such approval as stated in the approval letter from FDA, except that such a marketing application can be approved sooner if, and such time as, any of the following occurs:

(1) Withdrawal of exclusive approval or revocation of orphan-drug designation by FDA under any provision of this part; or

(2) Withdrawal for any reason of the marketing application for the drug in question; or

(3) Consent by the holder of exclusive approval to permit another marketing application to gain approval; or

(4) Failure of the holder of exclusive approval to assure a sufficient quantity of the drug under section 527 of the act and § 316.36.

(b) If a sponsor's marketing application for a drug product is determined not to be approvable because approval is barred under section 527 of the act until the expiration of the period of exclusive marketing of another drug product, FDA will so notify the sponsor in writing.

§ 316.34 FDA recognition of exclusive approval.

(a) FDA will send the sponsor (or, the permanent-resident agent, if applicable) timely written notice recognizing exclusive approval once the marketing application for a designated orphan-drug product has been approved. The written notice will inform the sponsor of the requirements for maintaining orphan-drug exclusive approval for the full 7-year term of exclusive approval.

(b) When a marketing application is approved for a designated orphan drug that qualifies for exclusive approval, FDA will publish in its publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" information identifying the sponsor, the drug, and the date of termination of the orphan-drug exclusive approval. A subscription to this publication and its monthly cumulative supplements is available from the Superintendent of Documents, Government Printing Office, Washington, DC 20402–9325.

§ 316.36 Insufficient quantities of orphan drugs.

(a) Under section 527 of the act, whenever the Director has reason to believe that the holder of exclusive approval cannot assure the availability of sufficient quantities of an orphan drug to meet the needs of patients with the disease or condition for which the drug was designated, the Director will so notify the holder of this possible insufficiency and will offer the holder one of the following options, which must be exercised by a time that the Director specifies:

(1) Provide the Director 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 quantities of the orphan drug within a reasonable time to meet the needs of patients with the disease or condition for which the drug was designated; or

(2) Provide the Director in writing the holder's consent for the approval of other marketing applications for the same drug before the expiration of the 7-year period of exclusive approval.

(b) If, within the time that the Director specifies, the holder fails to consent to the approval of other marketing applications and if the Director finds that the holder has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated, the Director will issue a written order withdrawing the drug product's exclusive approval. This order will embody the Director's findings and conclusions and will constitute final agency action. An order withdrawing the sponsor's exclusive marketing rights may issue whether or not there are other sponsors that can assure the availability of alternative sources of supply. Once withdrawn under this section, exclusive approval may not be reinstated for that drug.

Subpart E—Open Protocols for Investigations

§ 316.40 Treatment use of a designated orphan drug.

Prospective investigators seeking to obtain treatment use of designated orphan drugs may do so as provided in § 312.34 of this chapter.

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Subpart F—Availability of Information

§ 316.50 Guidelines.

FDA's Office of Orphan Products Development will maintain and make publicly available a list of guidelines that apply to the regulations in this part. The list states how a person can obtain a copy of each guideline. A request for a copy of the list or for any guideline should be directed to the Office of Orphan Products Development (HF-35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

§ 316.52 Availability for public disclosure of data and information in requests and applications.

(a) FDA will not publicly disclose the existence of a request for orphan-drug designation under section 526 of the act prior to final FDA action on the request unless the existence of the request has been previously publicly disclosed or acknowledged.

(b) Whether or not 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.

(c) Upon final FDA action on a request for designation, FDA will determine the public availability of data and information in the request in accordance with part 20 and § 314.430 of this chapter and other applicable statutes and regulations.

(d) In accordance with § 316.28, FDA will make a cumulative list of all orphan drug designations available to the public and update such list monthly.

(e) FDA will not publicly disclose the existence of a pending marketing application for a designated orphan drug for the use for which the drug was designated unless the existence of the application has been previously publicly disclosed or acknowledged.

(f) 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 and § 314.430 of this chapter and other applicable statutes and regulations.

Dated: May 21, 1992.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

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