• How can we modify, streamline, or expand our regulatory review process?

d. Prioritization

• How should we prioritize rules that are to be reviewed (*e.g.,* chronologically; based on rules where the greatest impact could be made from potential changes; rules with potential to have greatest savings in costs or paperwork/reporting burdens; rules with most potential for changes to enhance safety)?

3. Substance of Review

• Should the review include any or all of the considerations in RFA reviews (i.e., continued need for the rule; nature of complaints or comments concerning the rule; complexity of the rule; extent of overlap or conflicts with other federal (and possibly state and local) rules; and length of time since the rule has been evaluated; or extent of change in technology, economic conditions, or other factors)?

• Should we conduct cost-benefit analyses with every rule we review or only for significant rules as anticipated by the Executive Orders? Please explain your reasoning. Do commenters have suggestions for how we might develop our analysis of costs and benefits for rules under consideration for retrospective review?

Dated: October 12, 2011.

Todd A. Stevenson,

Secretary, Consumer Product Safety Commission.

[FR Doc. 2011–26820 Filed 10–18–11; 8:45 am]

BILLING CODE 6355–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 316

[Docket No. FDA–2011–N–0583]

RIN 0910–AG72

Orphan Drug Regulations

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the 1992 Orphan Drug Regulations issued to implement the Orphan Drug Act. These amendments are intended to clarify regulatory provisions and make minor improvements to address issues that have arisen since those regulations were issued.

DATES: Submit either electronic or written comments on the proposed rule by January 17, 2012. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by November 18, 2011 (see the ''Paperwork Reduction Act of 1995'' section of this document).

ADDRESSES: You may submit comments, identified by Docket No. FDA–2011–N–0583 and/or RIN number 0910–AG72, by any of the following methods, except that comments on information collection issues under the Paperwork Reduction Act of 1995 must be submitted to the Office of Regulatory Affairs, Office of Management and Budget (OMB) (see the ''Paperwork Reduction Act of 1995'' section of this document).

Electronic Submissions

Submit electronic comments in the following way:

• *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

• *Fax:* 301–827–6870.

• *Mail/Hand delivery/Courier (for paper, disk, or CD–ROM submissions):* Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA–2011–N–0583 and Regulatory Information Number (RIN) 0910–AG72 for this rulemaking. All comments received may be posted without change to *http://www.regulations.gov,* including any personal information provided. For additional information on submitting comments, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Erica K. McNeilly, Office of Orphan Products Development, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, rm. 5271, Silver Spring, MD 20993, 301–796–8660.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background

Since the publication of the Orphan Drug Regulations in the **Federal Register** of December 29, 1992 (57 FR 62076), FDA has reviewed over 3,350 requests for orphan-drug designation of drugs for rare diseases and conditions. Based on these experiences, FDA believes it is useful to clarify certain regulatory language in the current orphan drug regulations and to propose areas of minor improvement. These amendments are intended to assist sponsors who are seeking and who have obtained orphan-drug designation of their drugs, as well as FDA in administering the orphan drug program. These amendments are consistent with the Orphan Drug Act (Pub. L. 97–414) and continue to provide incentives for the development of potentially promising orphan drugs that otherwise would not be developed for rare diseases and conditions.

The specific issues addressed in this proposal include: (1) Demonstration of an appropriate ''orphan subset'' of persons with a particular disease or condition that otherwise affects 200,000 or more persons in the United States, for the purpose of designating a drug for use in that subset; (2) eligibility for

orphan-drug designation of a drug that is otherwise the same drug for the same orphan indication as a previously approved drug; (3) eligibility for multiple orphan-drug exclusive approvals when a designated orphan drug is separately approved for use in different subsets of the rare disease or condition; (4) requirement for demonstrating clinical superiority for the purpose of orphan-drug exclusive approval; (5) requirement for submitting the name of the drug in an orphan-drug designation request; (6) required drug description and scientific rationale in a designation request; (7) required information in a designation request relating to the sponsor's interest in the drug; (8) timing of a request for orphan-drug designation; (9) responding to a deficiency letter from FDA on an orphan-drug designation request; (10) FDA publication of information regarding designated orphan drugs; (11) FDA recognition of orphan-drug exclusive approval; (12) miscellaneous terminology changes; and (13) an address change.

II. Description of the Proposed Changes

A. Demonstration of an ''Orphan Subset'' of a Disease or Condition

As set forth in part 316 (21 CFR part 316), a sponsor may request orphan-drug designation of a drug for use in persons with a rare disease or condition or, in some special circumstances, a subset of persons with a disease or condition that may not otherwise be rare (hereinafter, a ''non-rare'' disease or condition). With respect to the latter, § 316.20(b)(6) stipulates that when a drug is to be developed for only a subset of persons with a particular disease or condition, the sponsor must provide ''a demonstration that the subset is medically plausible.'' This concept has been the subject of some confusion, and FDA has received requests for further clarification.

The term ''medically plausible'' subset used in § 316.20(b)(6) refers to a regulatory concept specific to the orphan drug regulations. The applicability of this regulatory concept is explained in section II.B of the preamble to the notice of proposed rule making (NPRM) entitled ''Orphan Drug Regulations'' published in the **Federal Register** of January 29, 1991 (56 FR 3338 at 3339). Because the term ''medically plausible'' has not been further clarified through regulations or guidance, it has been misinterpreted to mean any medically recognizable or any clinically distinguishable subset of persons with a particular disease or condition. Inappropriate application of the concept of a ''medically plausible'' subset could result in the creation of subsets of non-rare diseases or conditions that are artificially narrow. This result would be inconsistent with the purpose of the Orphan Drug Act.

For example, some requests for orphan-drug designation have been for use of a drug in a subset of persons with a particular pathohistologic grade or clinical stage of a specific malignancy, but without a plausible argument why the drug could not be used to safely treat all persons with the malignancy, regardless of disease grade or stage. Another example of misinterpretation of the term ''medically plausible'' has been its application to a select group of persons with a disease or condition who are eligible to enroll in a clinical trial to support a specific indication for use of a drug when there is no scientific reason to preclude investigational use of the drug in other persons with the disease or condition. Patients who meet inclusion and exclusion criteria for a trial do not automatically qualify as a ''medically plausible'' subset because it could be medically appropriate to evaluate the same drug for use in the remaining persons with the same disease or condition. Similarly, a sponsor's intention to use or study a drug in a certain limited group of persons with a non-rare disease or condition does not necessarily qualify that group as a ''medically plausible'' subset.

Any of the interpretations described in the previous paragraphs would permit a non-rare disease or condition to be artificially subdivided into smaller groups for the purpose of establishing subsets that are under the prevalence limit for orphan-drug designation. FDA does not believe that such an approach serves the intent of the Orphan Drug Act, because it would permit the creation of artificial ''orphan'' populations. Designation of drugs for use in such artificial ''orphan'' populations could encourage sponsors to study and seek approval for the use of a drug in the narrowest patient group possible, in order to avail themselves of the orphan-drug incentives, including tax benefits and orphan-drug exclusive approval. In addition, use of such artificial orphan populations to obtain orphan designation and its related benefits could divert resources away from research and development of drugs for true orphan diseases and conditions.

To limit the confusion arising from the use of the term ''medically plausible,'' FDA proposes to remove the term ''medically plausible'' in § 316.20(b)(6) and instead provide a description of how an appropriate subset may be identified for the purpose of orphan-drug designation (''orphan subset''). The process for identifying an orphan subset remains the same as has been used by FDA for identifying a medically plausible subset under the regulations currently in effect.

For a subset of persons with a non-rare disease or condition to be considered an orphan subset for the purpose of orphan-drug designation, the subset cannot be arbitrarily chosen simply to reduce the prevalence numbers to qualify a drug to treat that population as an orphan drug. One way for a sponsor to demonstrate that the proposed subset rests on a non-arbitrary foundation is to show that there is a reasonable scientific or medical rationale for limiting the investigation and potential use of the drug to only the subset of interest. When a sponsor has established that the selected population constitutes a non-arbitrary subset, *e.g.,* by describing the scientific or medical basis for limiting the potential use of the drug to that population and demonstrating that such scientific or medical basis is reasonable, the target population is an acceptable orphan subset of persons with the particular disease or condition for the drug of interest.

For example, it might not be appropriate to treat all persons with a non-rare disease or condition with a drug that is highly toxic; however, those patients who are refractory to, or intolerant of, other less toxic drugs might be reasonable candidates for treatment with the drug. Therefore, those patients who are refractory to, or intolerant of, other less toxic drugs may be considered an appropriate orphan subset for purposes of orphan-drug designation of the highly toxic drug. In addition, other inherent properties of a drug, such as its pharmacologic or biopharmaceutical characteristics, may provide a reasonable basis upon which to identify a subset of patients to whom it would be appropriate to limit treatment and who thus would qualify as an orphan subset of a non-rare disease or condition. Likewise, characteristics of the drug that have been demonstrated through previous clinical experiences may be used to identify an appropriate orphan subset. Examples of such characteristics include:

- *Pharmacological Property:* The mechanism of action is a common principle for limiting the investigation and use of a drug to a subset of patients. For example, it is reasonable to expect that use of a monoclonal antibody directed against a specific surface antigen would be restricted to treatment

of subtypes of tumors that possess that specific antigen, and not subtypes of tumors that lack the antigen.

• *Previous Clinical Experience:* Information on the drug's activity available from completed trials or published in clinical literature may be used to establish an orphan subset. If, for example, relevant data show that the drug has no significant activity in the remaining subset of patients with high-grade tumors, then patients with low-grade tumors may constitute an orphan subset.

FDA recommends that the following practical questions be asked when assessing whether a subset of a non-rare disease or condition is an appropriate orphan subset:

• Is the intended subset artificially restricted in any way with respect to the use of the drug to treat the disease or condition?

• Given that the drug may potentially benefit this particular subset of persons, is there a reasonable scientific or medical basis for believing that the drug would also potentially benefit the remaining population with the non-rare disease or condition or a larger subset of that population? If not, why not?

These questions serve to test whether a subset of patients with a disease or condition that otherwise affects 200,000 or more persons in the United States can be considered an appropriate orphan subset for the purpose of orphan-drug designation.[1]

B. Eligibility for Orphan-Drug Designation of a Drug That Was Previously Approved for the Orphan Indication

According to §§ 316.20(a) and 316.25(a)(3), a sponsor of a subsequent drug that is otherwise the same drug as an already approved orphan drug may seek and obtain orphan-drug designation of its drug for the same rare disease or condition, provided that it can present a plausible hypothesis that the subsequent drug may be clinically superior to the approved orphan drug. In the absence of a clinical superiority hypothesis, the Agency does not interpret the orphan-drug regulations to permit orphan designation of a drug that is otherwise the same as a drug that is already approved for the orphan use, either where the approved drug received orphan-drug exclusive approval (even after such drug's exclusivity period has run out) or where the approved drug was not previously designated as an orphan drug and thus did not receive orphan exclusive approval. If the same drug has already been approved for the orphan disease or condition, with or without orphan exclusivity, designation would be inappropriate because it would be inconsistent with the primary purpose of the Orphan Drug Act, which is to provide incentives to develop promising drugs for rare diseases or conditions that would not otherwise be developed and approved. Furthermore, permitting orphan-drug designation of a drug that is already approved for the orphan indication could permit inappropriate ''evergreening'' of exclusive approval periods. For example, a sponsor might obtain approval and 5-year new chemical entity exclusivity as described in § 314.108 (21 CFR 314.108) for a drug product and then, once that 5-year exclusivity period is expiring, seek orphan-drug designation and exclusive approval for a drug that is the same as the drug (*e.g.,* in a new dosage form) for the same indication that was previously approved. This outcome would be inconsistent with the provisions of the Orphan Drug Act, which provide that exclusive approval for a drug for an orphan disease or condition runs for 7 years from the date of approval of the application for the drug (21 U.S.C. 360cc(a)).

Accordingly, FDA proposes to delete the word ''orphan'' in the phrase ''approved orphan drug'' in §§ 316.3(b)(3), 316.20(a), and 316.20(b)(5), to clarify that these provisions would be applicable to a drug that is otherwise the same drug as *any* previously approved drug for the same orphan disease or condition, regardless of whether such drug was designated as an orphan drug. FDA proposes that the text of § 316.25(a)(3) be revised. FDA is not changing its position that, as described in the NPRM preamble (56 FR 3338), section II.E, paragraph 8, ''even a drug considered the 'same' drug structurally could become a 'different' drug * * * by showing clinical superiority.'' In section II.I, comment 77, of the preamble to the final rule, ''Orphan Drug Regulations'' (57 FR 62076 at 62084), FDA reiterated that it would ''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.' '' FDA believes that permitting a sponsor to receive orphan-drug designation of a potentially clinically superior drug that is otherwise the same drug as an already approved drug promotes development of potentially superior drugs to the benefit of persons with rare diseases or conditions.

C. Eligibility for Multiple Orphan-Drug Exclusive Approvals

When FDA designates an orphan drug, it generally designates the drug for use by all persons with the rare disease or condition and expects that a sponsor will seek approval of the drug for all persons with the rare disease or condition designated. The uses for which a drug will be approved, however, are those for which there is adequate data and information to support approval, and may be limited to subsets of patients with the orphan disease or condition. As new data emerge, FDA may approve the drug for use in additional subsets of the disease or condition for which the drug was designated.

The scope of orphan exclusive approval for a designated drug is limited to the approved indication or use, even if the underlying orphan designation is broader. If the sponsor who originally obtained orphan exclusive approval of the drug for only a subset of the orphan disease or condition for which the drug was designated subsequently obtains approval of the drug for one or more additional subsets of that orphan disease or condition, FDA will recognize orphan-drug exclusive approval, as appropriate, for those additional subsets from the date of such additional marketing approval(s). Before obtaining such additional marketing approval(s), the sponsor in this instance would not need to have obtained additional orphan designation for the additional subset(s) of the orphan disease or condition.

If, before approval of the drug for any subset of the disease or condition for which it was designated, a subsequent sponsor also obtained designation for the same orphan disease or condition, each sponsor may be eligible for orphan-drug exclusive approval for the respective subset(s) for which each first obtains marketing approval. For example, if the first sponsor receives approval for one subset of the orphan disease or condition and the subsequent sponsor receives approval for a different subset, FDA will recognize orphan-drug exclusive approval for each sponsor's drug, as appropriate, from the date of each drug's marketing approval.

[1] In this proposed rule, FDA is not proposing to change the current regulatory provisions allowing sponsors to obtain orphan-drug designation for a drug intended for a disease or condition affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 200,000 or more people per year, if there is no reasonable expectation that research and drug development costs can be recovered by sales of the drug in the United States (§§ 316.20(b)(8)(ii) and 316.21(c)).

After approval of the drug for one or more subsets of the orphan disease or condition, a subsequent sponsor may, without submitting a plausible hypothesis of clinical superiority, seek designation of the drug for the subset(s) of the orphan disease or condition for which the drug has not yet been approved. FDA may designate the drug for use in the remaining subset(s) without requiring a postulation of clinical superiority. To obtain such a designation, however, the sponsor must demonstrate that, at the time of its designation request, the entire population with the orphan disease or condition, not just the remaining subset(s) of the population, is under the prevalence limit, unless the sponsor can demonstrate that the remaining subset(s) is an orphan subset in accordance with § 316.20(b)(6).

This approach would permit multiple orphan-drug exclusive approvals for multiple subsets of the same underlying orphan disease or condition. For example, a drug could be designated for the treatment of T-cell non-Hodgkin's lymphoma (assuming that, at the time of designation, the drug's sponsor otherwise met all the other statutory and regulatory requirements for obtaining an orphan designation). However, the data submitted may only support approval of the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma. Subsequently, on the basis of additional data, the same drug could be approved for other subsets of T-cell non-Hodgkin's lymphomas, such as anaplastic large cell lymphoma or angioimmunoblastic T-cell lymphoma. If the same sponsor, or a different sponsor with orphan designation, obtained approval for the use of the drug in one or more of the remaining subsets of T-cell non-Hodgkin's lymphomas, that sponsor would be eligible for orphan-drug exclusive approval for the use of the drug in those subsets from the date of approval of the drug for use in those subsets. Accordingly, FDA proposes to add provisions to § 316.31.

FDA believes that this proposal is consistent with the purpose of the Orphan Drug Act because it provides an important incentive for one or more sponsors to develop, or to continue to develop, a potentially promising drug for use in all persons affected by a rare disease or condition, rather than in just a subset of that orphan population, even after the drug has been approved for a different subset of the population with the disease or condition.

This provision is applicable only in situations where the underlying disease or condition for which the drug was designated is an orphan disease or condition at the time designation is requested.

D. Demonstration of Clinical Superiority

FDA believes that granting orphan-drug designation to a subsequent drug that is otherwise the same as a previously approved drug for the same orphan disease or indication on the basis of hypothetical plausibility of clinical superiority is the best tool for giving effect to the intent of Congress to provide incentives for sponsors to develop potentially safer and more effective orphan drugs. It is possible, however, that a sponsor that has obtained designation of its drug on the basis of a hypothesis that the drug will be clinically superior will be unable, upon submission of the marketing application, to demonstrate that the drug is clinically superior to the previously approved drug. In that case, if the already approved drug has remaining exclusive approval, the subsequent drug would not itself be eligible for approval, because it is the same drug as the drug with exclusive approval. If the approved drug does not have exclusive approval, the subsequent drug may be approved, but would not itself be eligible for orphan-drug exclusive approval.

As described in § 316.3(b)(3)(i) and (b)(3)(ii), a drug that is otherwise the same drug as a previously approved drug, and for which a clear showing of greater effectiveness or greater safety has not been made, may still be considered clinically superior within the meaning of § 316.3(b)(3)(iii) if it makes a major contribution to patient care. FDA believes that such clinical superiority is meaningful only when the subsequent drug provides safety or effectiveness comparable to the approved drug. For example, to claim that a drug makes a major contribution to patient care through a new formulation or a different route of administration, the sponsor must also address whether the change renders the drug less safe or less effective than the approved drug. For these reasons, FDA proposes that § 316.3(b)(3)(iii) be revised.

E. Name of the Drug

As provided in § 316.20(b)(2), requests for orphan designation must include the generic and trade name, if any, of the drug. For some products, however, neither a generic, nor trade name may be available, for example, for some large and complicated biological products or for any molecule for which the sponsor has not yet obtained a trade name. FDA is proposing to revise § 316.20(b)(2) so that, if neither such name is available, requests for designation include a chemical name or a meaningful descriptive name (*i.e.,* one that would be meaningful to the public if published). By providing such information in the request for designation, sponsors would help ensure that the name that FDA ultimately publishes under § 316.28 upon designation of the product is accurate and meaningful.

F. Required Drug Description and Scientific Rationale in a Request for Orphan-Drug Designation

FDA needs adequate information on the drug to conduct the review of a request for orphan-drug designation. The identity of the active moiety or principal molecular structural features is of particular importance because such information is critical in determining whether various drugs are the same within the meaning of § 316.3(b)(13). FDA notes that a number of sponsors have omitted such information in their designation requests. Without such information, FDA cannot determine whether the drug is the same as one already approved and so cannot render a decision on the request.

FDA further notes that some sponsors have included in their designation requests only theories, unsupported by data, as to why the drug may be used in a particular disease or condition, which does not constitute an adequate scientific rationale for the use of the drug for the rare disease or condition. Other sponsors, by contrast, have included all available data about a drug, rather than just the data pertinent to demonstrating a scientific rationale to establish a medically plausible basis for the use of the drug for the rare disease or condition. Among the data pertinent to a request that should be included are in vitro data, preclinical efficacy data of the drug from studies conducted in a relevant animal model for the human disease or condition, and clinical data from use of the drug in the rare disease or condition. Animal toxicology studies are generally not relevant to a request for orphan-drug designation. To ensure that an adequate drug description and scientific rationale are provided in a request, along with the necessary supporting data (whether positive, negative, or inconclusive), FDA proposes to revise § 316.20(b)(4).

G. Removal of Requirement To Submit Statement as to Whether Sponsor Submitting the Request Is the Real Party in Interest

FDA regulations at § 316.20(b)(9) currently require that requests for

orphan-drug designations include 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. FDA is proposing to remove this requirement because it has proven to be of marginal if any utility in applications, has caused confusion for sponsors, and has had the effect of discouraging agents of sponsors (*e.g.,* a sponsor's lawyer) from submitting requests on the sponsor's behalf. Accordingly, FDA proposes to remove § 316.20(b)(9).

H. Timing of Request for Orphan-Drug Designation

FDA regulations at § 316.23(a) state that 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. FDA is aware that this language has been the subject of different interpretations by sponsors. To clarify the requirements regarding the timing of a designation request, FDA proposes to revise § 316.23(a) to indicate that a sponsor may request orphan-drug designation at any time in its drug development process prior to the time that sponsor submits a marketing application for the drug for the rare disease or condition. This is intended to clarify that a sponsor may not submit an orphan-drug designation request after it has submitted a marketing application for the drug for that use. This revision is also intended to clarify that submission by a sponsor of a marketing application for the drug for the orphan indication does not prevent another sponsor from submitting a request for orphan designation of the same drug for the same orphan use. Permitting designation of the subsequent drug in this situation, where there is no certainty that the previous marketing application will be approved promptly, if at all, would be consistent with the purpose of the Orphan Drug Act to provide incentives to develop and obtain approval for promising drugs for rare diseases or conditions. Once any sponsor's marketing application for the orphan indication has been approved, with or without orphan exclusive approval, another sponsor may not obtain orphan-drug designation for the same drug and the same orphan indication or use for which the approval was granted absent a plausible hypothesis of clinical superiority.

I. Responding to a Deficiency Letter From FDA on an Orphan-Drug Designation Request

FDA regulations are currently silent on when sponsors must respond to a deficiency letter from FDA on an orphan-drug designation request. FDA sends such deficiency letters when a request lacks necessary information or contains inaccurate information, for example, a miscalculated prevalence estimate. FDA has observed that some sponsors respond promptly to such deficiency letters, providing the requested information, whereas other sponsors may take several years or more to respond without sending any interim communication to FDA. In FDA's experience, when a period of several years or more elapses between the sponsor's initial request and the sponsor's deficiency response, the very basis for the orphan request may no longer hold in some circumstances. One example is if the initial request lacks an accurate prevalence estimate and the sponsor takes several years or more to submit a revised prevalence estimate keyed to the time of submission of the initial request, several years prior. In some circumstances, the actual prevalence for the disease or condition in question may have grown in the intervening years to exceed the prevalence limit of under 200,000. Because orphan designation eligibility in terms of prevalence is evaluated at the time of the submission of the request (see § 316.21(b)), the drug may be granted orphan-drug designation despite this prevalence increase, without any justification that there is no reasonable expectation of cost recovery (see §§ 316.20(b)(8)(ii) and 316.21(c)). FDA believes that such designations may be inconsistent with the purpose of the Orphan Drug Act, to provide incentives for the development of drugs for ''rare diseases or conditions'' as defined in section 526 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360bb).

To address this issue, FDA is proposing to require that sponsors respond to a deficiency letter within 1 year after issuance of the letter, unless within that timeframe the sponsor requests in writing an extension of time to respond. Such a request would specify both the reason(s) for the requested extension and the length of time of the requested extension. FDA will grant all reasonable requests for an extension. In some cases, FDA may grant a repeat request for an extension if, before expiration of the deadline as originally extended, the sponsor submits a new extension request, stating both the reason(s) for the request and the requested length of time of the extension.

In the event the sponsor fails to respond to the deficiency letter or to request an extension of time within a year, FDA may consider the designation request voluntarily withdrawn at the conclusion of the 1-year period, unless notified sooner by the sponsor that the request is withdrawn. FDA encourages sponsors to notify the Agency as soon as possible after receipt of a deficiency letter in the event the sponsor decides not to pursue the designation request. Should FDA deny a request for an extension of time, FDA may likewise consider the designation request voluntarily withdrawn and will so notify the sponsor in writing.

In FDA's experience, some deficiencies may be less suitable to extension requests than others. For example, FDA generally expects that deficiencies involving an inaccurate or incomplete prevalence estimate will be readily addressed within 1 year. Other types of deficiencies, however, may take longer to address. For example, deficiencies involving the scientific or medical rationale supporting a designation request for only a subset of persons with a particular disease or condition may require sponsors to conduct research and develop additional data, which may take several years or more. For the latter types of deficiencies, FDA generally anticipates granting extension requests to allow sponsors to develop necessary supporting data and information.

To implement this policy, FDA proposes to add new language to § 316.24(a). FDA proposes to change the title of this section to, ''Deficiency letters and granting orphan-drug designation.'' The existing paragraphs (a) and (b) would be redesignated (b) and (c), respectively.

J. Publication of Orphan-Drug Designations

Section 316.28 requires that FDA publish a monthly updated list of designated drugs in addition to placing on file at the FDA Division of Dockets Management an annual cumulative list of all designated drugs. FDA currently makes available a cumulative list of all designated drugs to date and a cumulative list of designated drugs in the current year on its Web site at *http://www.fda.gov/orphan/.* These lists are updated monthly.

To identify a drug in these lists and in the docket, FDA publishes its generic name and trade name, if any. If neither name is available, FDA publishes the chemical name or a meaningful

descriptive name of the drug (*i.e.,* a name that would be meaningful to the public). Internal business codes or other similar identifiers do not suffice for publication purposes, because they do not provide meaningful notice to the public of a designation. The Orphan Drug Act requires that notice respecting designation of a drug be made available to the public (section 526(c) of the FD&C Act). Ensuring that notice is meaningful, such that patients, health care providers, sponsors, and other stakeholders can identify which drug has been designated as an orphan drug, accords with both the language and the purpose of this statutory provision.[2] FDA proposes to revise § 316.28 to reflect FDA's existing publication practices.

The presence of a drug on the list of designated drugs does not necessarily mean the sponsor is actively developing the drug for the orphan disease or indication. Holders of orphan-drug designations are required by § 316.30 to submit an annual progress report on their designated drugs. It has been the Agency's experience that a number of holders of orphan-drug designations have failed to submit annual reports as required for the designated drug, and some have terminated their orphan-drug development program without notifying FDA. The Agency is considering ways to make available to the public information about the status of development for designated orphan drugs, including whether to provide information to the public on whether a sponsor has submitted the required annual reports. Although the failure of a sponsor to submit an annual report does not necessarily signal that the sponsor has ceased development of the orphan drug, this information could nevertheless prove useful to patients, medical practitioners, and the drug development community, who may wish to obtain additional information regarding the status of drug development from the sponsor of the designated drug.

Whether FDA will need to consider making additional information about designated drugs available through, for example, publishing the status of annual report submissions will depend in part on the effect of recent and pending changes in the availability of information about clinical trials of drugs. It is possible that expansion of the public availability of clinical trial information under section 801 of the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110–85) will provide the public additional useful information on whether trials of a designated drug are being undertaken for the orphan indication. The information derived from this clinical trials database may be as useful, or even more useful, to patients and other interested parties as would information on whether a sponsor had submitted an annual report as required.

We are seeking comment on whether it would be useful for the Agency to make public information about whether the sponsor of a designated drug has submitted annual reports as required under § 316.30. The Agency does not contemplate disclosing the contents of the annual report, only whether such annual report has been submitted.

K. FDA Recognition of Orphan-Drug Exclusive Approval

Under existing Agency practice, FDA does not recognize orphan-drug exclusive approval if the drug is otherwise the same drug as one already approved and the sponsor fails to substantiate, in the application for marketing approval, the hypothesis of clinical superiority over the previously approved drug that formed the basis for designation. To clarify existing practice, FDA proposes to add new language to § 316.34(c).

L. Miscellaneous Terminology Changes

FDA proposes to revise the following terms throughout part 316 for the sake of precision and internal consistency, so that each term is used consistently throughout this part: ''drug product'' versus ''drug,'' and ''indication'' and ''indicated'' versus ''designation,'' ''use,'' ''developed,'' and ''disease or condition.''

M. Address Change

FDA proposes to update the address in § 316.4 to ''Office of Orphan Products Development, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, Rm. 5271, Silver Spring, MD 20993.''

III. Environmental Impact

FDA has determined under 21 CFR 25.30(h) and 25.31(a) 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.

IV. Legal Authority

FDA is proposing this rule under the authority granted it by the Orphan Drug Act (Pub. L. 97–414). In enacting the Orphan Drug Act, Congress required FDA to issue regulations for the implementation of sections 525 and 526 of the FD&C Act (21 U.S.C. 360aa and 360bb), relating to written FDA recommendations on studies required for approval of marketing applications of orphan drugs and for the designation of eligible drugs as orphan drugs. In the **Federal Register** of December 29, 1992 (57 FR 62076) (1992 final rule), FDA issued a final rule for the implementation of these sections as well as for the implementation of sections 527 and 528 of the FD&C Act (21 U.S.C. 360cc and 360dd), relating 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. Any final rule based on this proposed rule would clarify regulatory provisions in the 1992 final rule and make minor improvements to address issues that have arisen since that rule took effect.

A final rule based on this proposal would further the main purpose of the Orphan Drug Act to provide incentives to develop promising drugs for rare diseases or conditions that would otherwise not be developed and approved. It would do so in several ways: By enhancing clarity for sponsors in seeking orphan-drug designations and orphan-drug exclusive marketing approval; by providing an important incentive for one or more sponsors to develop, or to continue to develop, a potentially promising drug for use in all persons affected by a rare disease or condition, rather than in just a subset of that orphan population, even after the drug has been approved for a different subset of the population with the disease or condition; and by helping ensure that the orphan designation request, at the time it is granted, is consistent with the purpose of the Orphan Drug Act despite a lapse of time between the date of submission of the initial request and a sponsor's response to a deficiency letter from FDA.

An additional source of authority for this proposed rule is section 701 of the FD&C Act (21 U.S.C. 371). Under this section, FDA is authorized to issue regulations for the efficient enforcement of the FD&C Act. Any final rule based on this proposed rule would help the efficient enforcement of the Orphan Drug Act provisions by enhancing clarity and certainty in FDA's

[2] In enacting and later amending the Orphan Drug Act, Congress emphasized the importance of effective public dissemination of orphan designation and the need for certainty about an orphan drug's potential for exclusivity (see H.R. Rep. No. 97–840, at 9 (1982), and H.R. Rep. No. 100–473, at 5–6 (1987)).

administration of the orphan drug program.

V. Proposed Implementation Plan

FDA proposes that these regulatory changes, where applicable, would become effective 30 days after the date of publication of the final rule. The final rule would apply only to original orphan-designation requests submitted on or after the effective date of the final rule. It would not apply to the following: (1) Amendments submitted on or after the effective date regarding previously submitted designation requests, or (2) responses to deficiency letters submitted on or after the effective date regarding previously submitted requests. As proposed here, the final rule would have no effect on the scope of or eligibility for orphan-drug exclusive approval because it merely clarifies existing FDA practice.

VI. Executive Order 13132: Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized, would not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency tentatively concludes that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VII. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). A description of these provisions is given in the *Description* section of this document an estimate of the annual reporting 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 each collection of information.

FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques and other forms of information technology, when appropriate.

Title: Orphan Drug Regulations.

Description: FDA is proposing to amend its regulations on orphan-drug designation requests to clarify policy and make minor improvements. The proposed revisions are intended to assist sponsors who are seeking and who have obtained orphan-drug designations, as well as FDA in its administration of the orphan drug program.

One proposed revision is a requirement that sponsors include in requests a chemical or meaningful descriptive name of the drug, if neither a trade name nor a generic name is available. By providing such information in the request for designation, sponsors would help ensure that the name that FDA ultimately publishes under § 316.28 upon designation of the product is accurate and meaningful to the public. Because sponsors are already required to include a description of the drug in requests for designation, the proposed requirement to include a chemical or meaningful descriptive name is not expected to require much additional time or effort from sponsors.

Based on historical data concerning the number of designation requests for which neither a trade name nor a generic name for the drug is available, FDA expects that about 20 requests per year would be affected by this requirement. FDA estimates that it will take approximately 0.2 hours, or 12 minutes, for sponsors to submit this information. This estimate reflects both the length of time likely required to submit the chemical name of the drug (less than 0.2 hours) and the length of time likely required to submit a meaningful descriptive name if a chemical name is not readily available (more than 0.2 hours).

Another proposed revision is a requirement that sponsors respond to deficiency letters from FDA on designation requests within 1 year of issuance of the deficiency letter, unless within that timeframe the sponsor requests in writing an extension of time to respond. FDA will grant all reasonable requests for an extension. In the event the sponsor fails to respond to the deficiency or request an extension of time to respond within the 1-year timeframe, FDA may consider the designation request voluntarily withdrawn.

FDA believes this proposal is necessary to ensure that designation requests do not become ''stale'' by the time they are granted, such that the basis for the initial request may no longer hold. Granting such designations despite a lapse of years and change in factual circumstances concerning the disease or condition in question may not serve the primary purpose of the Orphan Drug Act to provide incentives for the development of drug products for ''rare diseases or conditions'' as defined in section 526 of the FD&C Act.

Based on historical data concerning the number of deficiency letters that FDA has sent and the number of sponsors who have taken longer than a year to respond, FDA estimates that it will receive approximately 10 written requests each year for an extension of time to respond. This number is likely an overestimate, because it is based on historical data in the absence of any regulatory deadline for sponsors to respond; FDA believes that at least some of the sponsors who have taken longer than a year to respond have been capable of responding earlier, but did not do so because they did not need to. FDA estimates that it will take approximately 2 hours to prepare and submit each extension request, including time to develop and articulate a rationale for the requested extension and to obtain internal approval of the request before submission to FDA.

Description of Respondents: Persons and businesses, including small businesses and manufacturers.

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN [1]

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
316.20(b)(2)	20	1	20	0.2 (12 minutes)	4
316.24(a)	10	1	10	2	20
Total Burden Hours					24

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Except with respect to the proposed revisions addressed in table 1 of this document, the revisions in this proposed rule clarify existing regulatory language and do not constitute a substantive or material modification to the approved collections of information in current part 316 (Cf. 5 CFR 1320.5(g)). The collections of information in current part 316 have been approved by OMB in accordance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520), under OMB control number 0910–0167.

To ensure that comments on information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, *Attn:* FDA Desk Officer, *FAX:* 202–395–6974, or e-mailed to *oira_submission@omb.eop.gov.* All comments should be identified with the title ''Orphan Drug Regulations.''

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3407(d)), the Agency has submitted the information collection provisions of this proposed rule to OMB for review. These requirements will not be effective until FDA obtains OMB approval. FDA will publish a notice concerning OMB approval of these requirements in the **Federal Register**.

VIII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Agency believes that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this proposed rule primarily clarifies current practice and any costs would be very small, the Agency proposes to certify that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and Tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year.'' The current threshold after adjustment for inflation is $136 million, using the most current (2010) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

A. Background

Our experience with orphan-drug designation requests over many years has led us to conclude that sponsors are confused by some portions of the current regulatory language. The Agency receives dozens of requests for orphan-drug designation each year that are deficient in some way that would prevent designation. We observe the same types of deficiencies suggesting some problematic areas in our regulations.

Of the 324 requests for orphan-drug designation we received in 2010, 124 were denied or placed in abeyance so that the sponsor could submit additional material to respond to the deficiencies. Of these, 79 were deficient because they did not identify an appropriate ''medically plausible subset'' of a population with a non-rare disease or condition. That nearly a quarter of the designation requests were deficient in the subset analysis, and that problems with population subsets constituted over half of the deficiencies, highlights the need to clarify existing regulatory language regarding subsets.

The confusion about regulatory language is not limited to issues regarding population subsets. Many designation requests are deficient because the submitted drug description is not adequate to establish whether the drug is the same as one that has already been approved. There are continuing problems with requests for drugs that are in fact the same as drugs already approved but lack necessary information regarding clinical superiority. Other requests lack the data to support the scientific rationale for the use of the drug in a rare disease or condition. Addressing these deficiencies and resolving sponsor inquiries consumes sponsor and FDA resources and extends the orphan-drug designation process. The process would be less costly to sponsors and FDA if sponsors had an authoritative source of information about basic program requirements.

Basic program requirements are part of Federal regulation; clarifying regulatory language to reduce costly confusion would have to be done through rulemaking at the Federal level. This proposed rule would clarify regulatory language to reduce sponsor and FDA costs and streamline the orphan-drug designation process.

B. Benefits and Costs of the Proposed Rule

This proposed rule would reduce costs to sponsors who might otherwise submit deficient orphan-drug designation requests or face additional costs to determine program requirements. It would benefit sponsors and promote public health by clarifying requirements for sponsors who would otherwise be discouraged from submitting designation requests when their drug is in fact eligible for orphan-drug designation. The proposed rule would also reduce costs to FDA of responding to sponsor inquiries and

deficient designation requests. There would be small costs associated with the requirement that sponsors either respond to deficiency letters within a year or obtain an extension of time to respond. The proposed rule has several elements, which we address in the order presented earlier in this document.

We propose to clarify what population or disease subsets may be eligible for orphan-drug designation (§ 316.20(b)(6)). This action merely clarifies longstanding policy but should reduce uncertainty about the requirements for orphan-drug designation and result in fewer requests that cannot be designated. With the improved information about requirements for establishing population subsets, some sponsors may realize that their drug is not eligible for orphan designation and they would save the cost they would have otherwise incurred submitting a request. FDA has recently estimated a burden of 150 hours to complete a designation request (76 FR 3910 at 3911, January 21, 2011). At a benefit-adjusted hourly wage of about $46 for a regulatory affairs official, sponsors who do not submit a request that cannot be granted would avoid $6,900 in labor costs.[3] Under this proposed rule, other sponsors would avoid the cost they would have otherwise incurred addressing the subset deficiency. We do not have a precise estimate of the time required to respond to a deficiency letter; using 40 hours as a rough estimate implies $1,840 in avoided labor costs. We do not possess a reliable estimate for the number of avoided deficiency letters, but assuming FDA receives 79 subset-deficient requests each year and one-half would not occur with the clarified regulatory language, sponsors would avoid $72,680 in additional labor costs. FDA would also avoid costs from responding to these requests.

It is longstanding FDA policy that a designation request for a drug that is otherwise the same as a drug previously approved for the same disease or condition must include a plausible hypothesis of clinical superiority, regardless of whether the already approved drug was designated as an orphan. FDA continues to receive requests that cannot be designated because this policy is not explicit in current regulation. This proposed rule would make this policy explicit, reducing costs to sponsors and FDA by reducing the number of deficient orphan-drug designation requests.

FDA's longstanding practice has been that if a drug is approved for only a subset of patients with a rare disease or condition, FDA may grant orphan-drug designation and orphan-drug exclusive approval for use of the drug in one or more of the remaining subsets of patients with the rare disease or condition. Current § 316.31 does not explicitly mention subsets, which could deter confused sponsors from pursuing designation for use of the drug in remaining subsets for which the drug has not yet been approved. Clarifying this provision would not change Agency policy but would benefit sponsors and public health by reducing the risk of a sponsor failing to pursue designation when it would otherwise do so.

We propose to clarify the definition of clinical superiority to make explicit that a drug shown to be clinically superior to an approved drug for making a major contribution to patient care would also have to be demonstrated to provide safety and effectiveness comparable to the approved drug (§ 316.3(b)(3)(iii)). This revision is consistent with longstanding policy and would impose no new costs. Benefits from a minor clarification to a requirement that applies only under unusual circumstances would be too small to reliably estimate.

We propose to modify and clarify our requirements for the drug name. Current regulations require the sponsor to submit the generic and trade name of the drug, but do not specify how to name a drug for which there is no generic name or trade name. In the past, sponsors have provided FDA with their internal business codes, which are meaningless to the general public. We propose to require that a drug that has neither a generic nor a trade name be identified according to its chemical name or a meaningful descriptive name (*i.e.,* one that would be meaningful to the public if published). Descriptive names are readily accessible to the sponsor and could be included in a designation request as easily as an internal business code and any costs would be too small to meaningfully quantify.

We propose to clarify our requirements for the drug description and for the data to support a drug's scientific rationale in an orphan-drug designation request. Some requests for orphan-drug designation cannot be acted upon because the drug descriptions are not adequate to determine whether the drug in the submission is the same as a previously approved drug. This proposed rule would clarify the required drug description in § 316.20(b)(4), reducing the frequency of deficient requests. Some requests lack the data to support a scientific rationale, while others include substantial additional data not needed to obtain designation. In both situations, sponsors incur costs that could be avoided with clearer requirements. We do not know the frequency of these data problems nor do we know the costs associated with them, but this proposal would reduce sponsor and FDA costs.

We propose to eliminate § 316.20(b)(9), which requires that the sponsor submitting the request state whether it is the real party in interest of the development and the intended or actual production and sales of the product. This provision merely obtains information from the sponsor; it does not provide a basis to disqualify any entity from pursuing orphan-drug designation. There is no known use for the information and it is our understanding that this provision may be discouraging sponsors from using agents to submit requests on their behalf, potentially increasing the cost to obtain orphan-drug designation. We do not possess a reliable estimate for this cost. Eliminating this provision would clarify our longstanding policy to accept submissions from agents, which may reduce sponsor costs. Halting the collection of information for which there is no known purpose would not negatively impact public health.

We propose to clarify the requirement regarding the timing of orphan-drug designation requests (§ 316.23(a)). A sponsor may not submit an orphan-drug designation request after it has submitted a marketing application for the drug for that use. It is not clear in the current regulatory language that one sponsor's marketing application would not prevent a different sponsor from submitting a request for orphan designation for the same drug for the same orphan use and that this subsequent sponsor would not have to submit a plausible hypothesis of clinical superiority. Clarifying current policy would benefit sponsors and public health by reducing the likelihood of a confused sponsor failing to seek orphan-drug designation for an eligible product.

We propose a 1-year time limit for sponsors to respond to deficiency letters or obtain a time extension (§ 316.24(a)). Based on our experience with the time required to address particular submission deficiencies and the observed variation in time for sponsors to respond, some submission requests

[3] 2010 National Industry-Specific Occupational Employment and Wage Estimates, U.S. Department of Labor Statistics, last modified May 17, 2011 (*http://www.bls.gov/oes/current/naics4_325400.htm*); mean compliance officer wage rate of $35.28 for pharmaceutical and medicine manufacturing (NAICS 325400) plus a 30-percent increase for benefits.

do not appear to be part of an active effort to obtain orphan-drug designation. We know of no public health benefit from open inactive designation requests. We do not know if they exist because sponsors gain nothing from the cost of formally withdrawing a request or because there may be a strategic advantage to an inactive request for designation. Current regulations do not impose time limits on sponsors replying to FDA deficiency letters and we have no mechanism to encourage sponsors to continue to actively pursue designation. Sponsors who would otherwise respond to a deficiency letter within 1 year would be unaffected by this proposal. Sponsors actively pursuing designation but needing more than 1 year to respond to a deficiency letter would be expected to submit a time extension request to FDA. We assume approval for all extension requests from sponsors actively pursuing orphan-drug designation and estimate a request would require 2 hours of time from a regulatory affairs specialist. At a benefit-adjusted hourly wage of $46, the cost to submit an extension request is $92. Based on our experience with deficiency letters and the frequency of responses requiring more than 1 year, we estimate 10 requests for additional time each year. The estimated annual cost of this provision is $920. We assume sponsors not actively pursuing designation would not obtain extensions and their requests would be considered to be withdrawn 1 year after the deficiency letter. We do not possess a reliable estimate of the number of designation requests that would be withdrawn under this proposal. Withdrawing inactive designation requests would improve information about potential future orphan drugs, which would be beneficial to potential sponsors and to the general public. There is at least a potential for a cost to some sponsors, as we cannot rule out the possibility of some small advantage to holding an inactive designation request. Nevertheless, we estimate the cost of a withdrawal in this case to be very small and to be extremely small relative to the benefits of improved public information and the streamlined orphan-drug designation process.

According to longstanding policy, FDA does not recognize orphan-drug exclusive approval when the sponsor of a drug that is otherwise the same as a drug already approved fails to demonstrate clinical superiority in its marketing application. We propose to make this policy explicit by adding proposed § 316.34(c). This clarification applies to a rare set of circumstances and benefits would be too small to reliably estimate.

We do not possess a single bottom line estimate for the total monetized benefit of this proposed rule. Avoiding half of the designation requests that are deficient because of problems establishing population subsets would save sponsors an estimated $73,000 annually. Subset problems account for more than half of all deficiencies, so we estimate the other clarifications to reduce deficient requests would reduce sponsor costs by an additional amount less than $73,000. The total estimated cost of this proposed rule is an annual $920, attributable to the submission of requests for additional time to respond to deficiency letters.

C. Small Business Analysis

This proposed rule would apply to the sponsors of orphan-drug designation requests. According to the Table of Small Business Size Standards, the U.S. Small Business Administration (SBA) considers pharmaceutical preparation manufacturing entities (NAICS 325412) with 750 or fewer employees and biological product (except diagnostic) manufacturing entities (NAICS 325414) with 500 or fewer employees to be small.[4] According to the 2007 Economic Census, annual shipments for the 284 establishments in NAICS 325412 with 0 to 4 employees are $240 million, which is $840,000 per establishment. Total annual shipments for the 250 establishments in NAICS 325414 with 0 to 49 employees (the smallest group with value of shipment data) are $720 million, which is $2.9 million per establishment.

Most of the provisions of this proposed rule would clarify regulatory language consistent with current practice, imposing no new costs. The proposal to create a 1-year time limit to respond to FDA deficiency letters would result in estimated costs of $92 per extension request. Costs from the withdrawal of inactive submissions would be too small to reliably quantify. A common threshold for determining a significant impact is 1 percent of annual shipments. Because the estimated cost of this proposed rule would be approximately 1/100 of 1 percent of annual shipments for the smallest affected establishments, we conclude this proposed rule, if finalized, would not constitute a significant impact on a substantial number of small entities.

[4] U.S. Small Business Administration, ''Table of Small Business Size Standards Matched to North American Industry Classification System Codes,'' November 5, 2010, *http://www.sba.gov/sites/default/files/Size_Standards_Table.pdf.*

IX. Request for Comments

Interested persons may submit to the Division of Dockets Management (*see* **ADDRESSES**) either electronic or written comments regarding this document. As noted previously in this document, if you have comments on specific provisions of the proposed regulation, we request that you identify these provisions in your comments. In addition, if you have concerns that would be addressed by alternative text for the regulation, we request that you provide this alternative text in your comments. It is only necessary to send one set of comments. It is no longer necessary to send two copies of mailed comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 316

Administrative practice and procedure, Drugs, Investigations, Medical research, Orphan drugs, Reporting and recordkeeping requirements.

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 proposed to be amended as follows:

PART 316—ORPHAN DRUGS

1. The authority citation for 21 CFR part 316 continues to read as follows:

Authority: 21 U.S.C. 360aa, 360bb, 360cc, 360dd, 371.

2. Section 316.1 is amended by revising paragraphs (a)(1)(iii) and (a)(2) to read as follows:

§ 316.1 Scope of this part.

(a) * * *

(1) * * *

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

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

* * * * *

3. Section 316.3 is amended by revising paragraphs (b)(3) introductory text, (b)(3)(i), (b)(3)(iii), and (b)(12) to read as follows:

§ 316.3 Definitions.

* * * * *

(b) * * *

(3) *Clinically superior* means that a drug is shown to provide a significant therapeutic advantage over and above

that provided by an approved drug (that is otherwise the same drug) in one or more of the following ways:

(i) Greater effectiveness than an approved 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

* * * * *

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

* * * * *

(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 for the same use for 7 years, except as otherwise provided by law or in this part.

* * * * *

4. Section 316.4 is revised to read as follows:

§ 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, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, rm. 5271, Silver Spring, MD 20993.

5. Section 316.20 is amended by revising paragraphs (a), (b)(2) through (b)(6), and by removing paragraph (b)(9), to read as follows:

§ 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 use for an already marketed drug. In addition, a sponsor of a drug that is otherwise the same drug as an already approved 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) * * *

(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, if neither is available, the chemical name or a meaningful descriptive name of the drug; 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 use of the drug, and the reasons why such therapy is needed.

(4) A description of the drug, to include the identity of the active moiety if it is a drug composed of small molecules, or of the principal molecular structural features if it is composed of macromolecules; its physical and chemical properties, if these characteristics can be determined; and a discussion of the scientific rationale to establish a medically plausible basis for the use of the drug for the rare disease or condition, including all data from in vitro laboratory studies, preclinical efficacy studies conducted in an animal model for the human disease or condition, and clinical investigations of the drug in the rare disease or condition that are available to the sponsor, whether positive, negative, or inconclusive. Animal toxicology studies are generally not relevant to a request for orphan-drug designation. 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 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 that otherwise affects 200,000 or more people, a demonstration that, due to one or more properties of the drug, the remaining persons with such disease or condition would not be appropriate candidates for use of the drug.

* * * * *

6. Section 316.21 is amended by revising paragraph (a)(1) and the introductory text of paragraph (b) to read as follows:

§ 316.21 Verification of orphan-drug status.

(a) * * *

(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 is to be developed is fewer than 200,000 persons; or

* * * * *

(b) For the purpose of documenting that the number of people affected by the disease or condition for which the drug is to be developed 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 developed, the sponsor shall submit to FDA evidence showing:

* * * * *

7. Section 316.23 is revised to read as follows:

§ 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 its drug development process prior to the time that sponsor submits a marketing application for the drug for the same rare disease or condition.

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

8. Section 316.24 is amended by revising the section heading; redesignating paragraphs (a) and (b) as (b) and (c), respectively; and adding a new paragraph (a), to read as follows:

§ 316.24 Deficiency letters and granting orphan-drug designation.

(a) FDA will send a deficiency letter to the sponsor if the request for orphan-drug designation lacks information required under §§ 316.20 and 316.21, or contains inaccurate or incomplete information. FDA may consider a designation request voluntarily withdrawn if the sponsor fails to respond to the deficiency letter within 1 year of issuance of the deficiency letter, unless within that same timeframe the sponsor requests in

writing an extension of time to respond. This request must include the reason(s) for the requested extension and the length of time of the requested extension. FDA will grant all reasonable requests for an extension. In the event FDA denies a request for an extension of time, FDA may consider the designation request voluntarily withdrawn and, if so, will notify the sponsor in writing.

* * * * *

9. Section 316.25 is amended by revising paragraphs (a)(1)(ii) and (a)(3) to read as follows:

§ 316.25 Refusal to grant orphan-drug designation.

(a) * * *

(1) * * *

(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 such disease or condition 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.

* * * * *

(3) The drug is otherwise the same drug as an already approved drug 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.

* * * * *

10. Section 316.26 is revised to read as follows:

§ 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 designated use if the proposed change is due to new and unexpected findings in research on the drug, 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 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.

11. Section 316.28 is revised to read as follows:

§ 316.28 Publication of orphan-drug designations.

Each month FDA will update a publicly available cumulative list of all drugs designated as orphan drugs. This list will be made available on the Agency's Internet site. In addition, a cumulative, annually updated list of all designated drugs will be placed on file at the FDA Division of Dockets Management. These lists will contain the following information:

(a) The name and address of the sponsor;

(b) The generic name and trade name, if any, or, if neither is available, the chemical name or a meaningful descriptive name of the drug;

(c) The date of the granting of orphan-drug designation; and

(d) The designated use in the rare disease or condition.

12. Section 316.31 is amended by revising paragraph (a) introductory text, by redesignating paragraph (b) as paragraph (c), and by adding new paragraph (b) to read as follows:

§ 316.31 Scope of orphan-drug exclusive approval.

(a) After approval of a sponsor's marketing application for a designated orphan drug for use in the rare disease or condition, or a subset thereof, concerning which orphan-drug designation was granted, FDA will not approve another sponsor's marketing application for the same drug for the same use 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 at such time as, any of the following occurs:

* * * * *

(b) Orphan-drug exclusive approval protects only the approved indication or use of a designated drug. If such approved indication or use is limited to a particular subset of persons with a rare disease or condition, FDA may later approve the drug for use in one or more additional subsets and, if the sponsor who obtains approval in the additional subset(s) has orphan-drug designation for the drug, FDA will recognize a new orphan-drug exclusive approval for the use in the new subset(s) of persons with the rare disease or condition from the date of approval of the drug for use in the new subset(s).

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13. Section 316.34 is amended by adding paragraph (c) as follows:

§ 316.34 FDA recognition of exclusive approval.

* * * * *

(c) If a drug is otherwise the same drug as a previously approved drug, FDA will not recognize orphan-drug exclusive approval if the sponsor fails to substantiate, at the time of marketing approval, the hypothesis of clinical superiority over the previously approved drug that formed the basis for designation.

Dated: October 13, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2011–27037 Filed 10–18–11; 8:45 am]

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DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[REG–146297–09]

RIN 1545–BJ23

Deduction for Qualified Film and Television Production Costs

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Notice of proposed rulemaking by cross reference to temporary regulation.

SUMMARY: In the Rules and Regulations section of this issue of the **Federal Register**, the IRS is issuing temporary regulations relating to deductions for the costs of producing film and television productions. Those temporary regulations reflect changes to the law made by the Tax Extenders and Alternative Minimum Tax Relief Act of 2008, and affect taxpayers that produce films and television productions within the United States. The text of those temporary regulations also serves as the text of these proposed regulations.

DATES: Written comments and requests for a public hearing must be received by January 17, 2012.

ADDRESSES: Send submissions to: CC:PA:LPD:PR (REG–146297–09), room 5205, Internal Revenue Service, P.O. Box 7604, Ben Franklin Station, Washington, DC 20044. Submissions may be hand delivered Monday through Friday between the hours of 8 a.m. and 4 p.m. to: CC:PA:LPD:PR (REG–146297–