

1. Memorandum from Hyoungh S. Lee, Division of Petition Review, Chemistry Review Team, to Raphael Davy, Division of Petition Review, Regulatory Group I, May 30, 2012.

2. Memorandum from Tina W. Walker, Division of Petition Review, Toxicology Team, to Raphael Davy, Division of Petition Review, Regulatory Group I, October 3, 2012.

List of Subjects in 21 CFR Part 73

Color additives, Cosmetics, Drugs, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, and redelegated to the Director, Center for Food Safety and Applied Nutrition, 21 CFR part 73 is amended as follows:

PART 73—LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION

■ 1. The authority citation for 21 CFR part 73 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e.

■ 2. Section 73.350 is amended by revising paragraph (c)(1) to read as follows:

§ 73.350 Mica-based pearlescent pigments.

* * * * *

(c) * * *

(1) The substance listed in paragraph (a) of this section may be safely used as a color additive in food as follows:

(i) In amounts up to 1.25 percent, by weight, in the following foods: Cereals, confections and frostings, gelatin desserts, hard and soft candies (including lozenges), nutritional supplement tablets and gelatin capsules, and chewing gum.

(ii) In amounts up to 0.07 percent, by weight, in distilled spirits containing not less than 18 percent and not more than 23 percent alcohol by volume but not including distilled spirits mixtures containing more than 5 percent wine on a proof gallon basis.

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Dated: June 6, 2013.

Susan M. Bernard,

Director, Office of Regulations, Policy and Social Sciences, Center for Food Safety and Applied Nutrition.

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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: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing final regulations amending 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: This rule is effective August 12, 2013.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

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I. Background

In the **Federal Register** of October 19, 2011 (76 FR 64868), FDA issued a proposed rule to amend the Orphan Drug Regulations (part 316 (21 CFR part 316)), to clarify certain regulatory language and propose areas of minor improvement regarding orphan-drug designation and orphan-drug exclusivity. The proposed rule addressed the following aspects of the Orphan Drug Regulations: (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 ("non-rare disease or condition"), for the purpose of designating a drug for use in that subset; (2) eligibility for designation of a drug that is otherwise the same drug for the same use as a previously approved drug; (3) eligibility for multiple orphan-drug exclusive approvals when a drug is designated for use in a rare disease or condition,¹ but is then separately approved for different indication(s) or use(s) within that particular rare disease or condition; (4) requirement for demonstrating clinical superiority for the purpose of orphan-drug exclusive approval when the drug is otherwise the same as a previously approved drug for the same use or indication; (5) requirement for submitting the name of the drug in a 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 orphan-drug designations; (11) FDA recognition of orphan-drug exclusive approval; (12) miscellaneous terminology changes; and (13) an address change.

FDA received comments on the proposed rule from 14 entities, mainly from companies and trade associations of companies that are marketing or hope to market orphan drugs. On the whole, the comments were strongly supportive of the orphan drug program and recognized the need for clarity in FDA requirements, though many comments raised objections to and questions about certain aspects of the proposed rule.

¹ Section 526(a) of the Federal Food, Drug and Cosmetic Act (FD&C Act) defines a "rare disease or condition" to include any disease or condition that affects fewer than 200,000 persons in the United States.

II. Overview of the Final Rule

This rule largely finalizes the revisions as proposed, with several changes for clarity and accuracy and one substantive change involving publication when a drug no longer has orphan-drug designation. The main changes from the proposed rule are as follows:

- Adding a definition of “orphan subset” to § 316.3(b)(13), using a definition that is consistent with the explanation of orphan subset in the proposed rule.
- Clarifying the existing regulation in accordance with FDA’s long-standing practice that a designated drug is eligible for orphan exclusive approval only if the same drug has not already been approved for the same use or indication,² by adding clarifying language to §§ 316.3(b)(12), 316.31(a), and 316.34(a).
- Removing the language in the proposed rule that, to demonstrate clinical superiority in terms of “major contribution to patient care” (§ 316.3(b)(3)(iii)), the drug must provide safety and effectiveness “comparable to the approved drug.” This language incorrectly implied that FDA would require direct proof of comparability to the already approved drug to demonstrate that a drug provides a major contribution to patient care (e.g., through non-inferiority trials).
- Adding an email address to the list of contact information required in requests for designation (§ 316.20(b)(2)), and making a related edit to the provision addressing the contact information required for permanent-resident agents (§ 316.22).
- Clarifying that a designation request need include only “relevant” *in vitro* laboratory data, as well as data from “clinical experience” with the drug in the rare disease or condition (§ 316.20(b)(4)). The proposal had omitted the qualifier “relevant” before *in vitro* laboratory data and had limited the clinical data to data from “clinical investigations.” FDA may in some cases consider other clinical data, such as well-documented case histories or significant human experience with the drug, as appropriate.
- Clarifying that, whenever FDA considers a designation request voluntarily withdrawn, FDA will notify the sponsor in writing (§ 316.24(a)). The proposal had erroneously implied that FDA would so notify the sponsor in writing only if the request was considered voluntarily withdrawn

because FDA had denied a sponsor’s request for an extension of time to respond to a deficiency letter, and not also if the sponsor had simply failed to respond, or request an extension of time to respond, within 1 year of issuance of the deficiency letter.

- Clarifying that, in addition to the reasons already expressly specified in § 316.25, FDA can refuse to grant a designation request if the request is otherwise ineligible for designation under part 316 (§ 316.25(b)). This revision merely codifies FDA’s longstanding interpretation.
- Stating that FDA’s publicly available posting of designated drugs will include whether a drug is no longer designated if the drug loses designation after the effective date of this final rule (§ 316.28). This information used to be deducible from FDA’s publication of hard copy quarterly lists of designated drugs: Drugs no longer designated would appear on earlier hard copy lists but not on later ones. Once FDA switched to Internet publication, this information was no longer deducible owing to database limitations at the time. FDA is also making a technical correction to § 316.28 to reflect that FDA no longer places an annual list of designated drugs on file at FDA’s Division of Dockets Management.
- Making explicit an option that has always existed for sponsors—that sponsors may voluntarily withdraw a designation request, or an actual designation, at any time by submitting a written request to FDA (§ 316.24(d)).
- Clarifying that the scope of orphan exclusive approval is limited to the indication(s) or use(s) for which the designated drug is approved (§ 316.31(a) and 316.31(b)). The proposal had used the term “subset” instead of “indication(s) or use(s)” (i.e., where a drug is approved for only a subset of patients with the rare disease or condition for which the drug is designated), which readers may have confused with the regulatory concept of “orphan subset” at § 316.20(b)(6). A reference to “orphan subset” was not intended at § 316.31. Orphan subset is a regulatory concept relevant to eligibility for orphan-drug designation, whereas this regulation at § 316.31 concerns the scope of orphan exclusive approval.
- Clarifying that a designated drug that is otherwise the same as a previously approved drug receives 7-years market exclusivity (“orphan-drug exclusivity”) upon approval only if the sponsor of the second-in-time drug demonstrates upon approval that its drug is clinically superior to the previously approved drug (§ 316.34(c)). This language corrects two possible

misinterpretations of the proposed rule, by clarifying that: (1) Sponsors may have to demonstrate clinical superiority to obtain orphan-drug exclusivity even if they did not have to submit a plausible hypothesis of clinical superiority to obtain designation (e.g., if the same drug is approved for the same use after the designation but before the approval of the sponsor’s drug); and (2) FDA will recognize orphan-drug exclusivity as long as clinical superiority to the previously approved drug is demonstrated, regardless of whether the sponsor substantiates the particular hypothesis of clinical superiority upon which designation was based (e.g., the drug may in fact be safer for a different reason than that hypothesized at the designation stage, or it may be demonstrated to be more effective instead of safer).

- Updating the FDA address listed at §§ 316.22 and 316.50 (in addition to doing so at § 316.4, as proposed) and adding an online address for the Orange Book at § 316.34(b).

This rule is 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. As described in the proposed rule (76 FR 64868), FDA believes these revisions will clarify, streamline, and improve the orphan-drug designation process. These amendments are fully consistent with the Orphan Drug Act (Pub. L. 97–414) and continue to provide incentives for the development of potentially promising orphan drugs that may not otherwise be developed and approved, including drugs that are potentially safer or more effective than already approved drugs.

III. Summary of and Response to Comments

FDA received comments on the proposed rule from 14 entities, mainly from companies and trade associations of companies that are marketing or hope to market orphan drugs. On the whole, the comments were strongly supportive of the orphan drug program and recognized the need for clarity in FDA requirements. Many comments also raised objections to and questions about certain aspects of the proposed rule, particularly the deletion of the phrase “medically plausible” from § 316.20 and clarification of the requirement for demonstrating clinical superiority to obtain orphan-drug exclusive approval.

Below, FDA responds to the comments in the order in which the sections were presented in the proposed rule. To make it easier to identify comments and our responses, the word

² Elsewhere in this preamble, we use the phrase “same use” as short-hand for “same use or indication.”

“Comment,” in parentheses, appears before the comment’s description and the word “Response,” in parentheses, appears before our response. We have numbered each comment to help distinguish between different comments. Similar comments are grouped together under the same number. The number assigned to each comment is purely for organizational purposes and does not signify the comment’s value, importance, or the order in which it was received.

*A. Demonstration of an “Orphan Subset” of a Non-Rare Disease or Condition*³

(Comment 1) Four comments objected to the proposal to delete “medically plausible” from the regulatory provision describing an orphan subset at § 316.20(b)(6), on the ground that this proposal would appear to narrow eligibility for orphan-drug designation. These comments asked FDA to retain “medically plausible” in the regulation.

(Response) FDA carefully considered whether to retain “medically plausible” in the regulatory provision describing an orphan subset at § 316.20(b)(6). Because of the confusion created by the term “medically plausible,” FDA decided to finalize the description of orphan subset as proposed. This confusion was manifest in the very comments objecting to the proposal and asking that the term “medically plausible” be retained.

As explained in the proposed rule (76 FR 64868 at 64869 to 64870), the term “medically plausible” has been misinterpreted by sponsors to mean any medically recognizable or clinically distinguishable subset of persons with a particular disease or condition—a misunderstanding reflected in some of the comments described previously. This misinterpretation of “medically plausible,” if accepted by FDA, could result in artificially narrow subsets for the purpose of orphan-drug designation. It could permit a non-rare disease or condition to be artificially subdivided into smaller groups for establishing subsets that are under the prevalence limit for designation. FDA does not believe that such an approach would serve the intent of the Orphan Drug Act, as explained in the proposed rule (76 FR

64868 at 64869 to 64870). Use of such artificial orphan populations to obtain orphan-drug designation and its related benefits would divert resources away from research and development of drugs for true orphan diseases and conditions. Further, it would encourage sponsors to study and seek approval for use of a drug in the narrowest possible artificial patient groupings within a disease or condition in order to avail themselves of the orphan-drug incentives, including tax benefits and orphan-drug exclusive approval, when other patients with the disease or condition would also benefit from use of the drug. Under this scenario, sponsors could even potentially “game” approvals by seeking successive narrow approvals of a drug to avail themselves of orphan-drug benefits when the overall approved use is not an orphan use. These outcomes would be inconsistent with the Orphan Drug Act.

By removing “medically plausible” from § 316.120(b)(6) and instead inserting a description of what orphan subset means, FDA aims to dispel the confusion created by the term “medically plausible.” This description is consistent with how FDA has long interpreted “medically plausible” in the context of orphan subsets. It is intended to make clear to sponsors that an orphan subset is a regulatory concept specific to the Orphan Drug regulations, and that it does not simply mean any medically recognizable or clinically distinguishable subset of persons with a particular disease or condition (as the term “medically plausible” in this context may have been erroneously interpreted to imply). Under FDA’s longstanding approach, eligibility for orphan subsets rests on whether use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but use of the drug outside of that subset (in the remaining persons with the non-rare disease or condition) would be inappropriate owing to some property(ies) of the drug, for example, drug toxicity, mechanism of action, or previous clinical experience with the drug. This is the same requirement as the requirement that FDA long employed for identifying “medically plausible” subsets for the purpose of orphan-drug designation. To be clear, FDA has never interpreted “medically plausible” to mean what these comments appear to claim it means. Thus, contrary to what these comments suggest, replacing “medically plausible” with a description of orphan subset will not result in a narrowing of eligibility for orphan-drug designation.

Partly in response to the confusion expressed by these comments, FDA is making a slight edit to § 316.20(b)(6) to

expressly incorporate the term “orphan subset.” In place of the opening clause, “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,” FDA is inserting the following language: “Where a sponsor requests orphan-drug designation for a drug for only a subset of persons with a particular disease or condition that otherwise affects 200,000 or more people (‘orphan subset’),” This edit has two advantages: it incorporates an overt reference to “orphan subset” into the regulatory language, and it clarifies that sponsors can seek designation of a drug for an orphan subset before they begin developing that drug. FDA is also adding “orphan subset” to the definition section at § 316.3(b)(13), as follows: “*Orphan subset of a non-rare disease or condition (‘orphan subset’)* means that use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but use of the drug outside of that subset (in the remaining persons with the non-rare disease or condition) would be inappropriate owing to some property(ies) of the drug, for example, drug toxicity, mechanism of action, or previous clinical experience with the drug.”

Finally, we note that we are retaining the term “medically plausible” elsewhere in part 316 when describing whether the scientific rationale for use of the drug for the rare disease or condition is adequate (§ 316.25(a)(2)) and whether the hypothesis of clinical superiority, if required, is plausible (§ 316.25(a)(3)). Unlike in the orphan subset context, the term “medically plausible” has not caused confusion among sponsors in these contexts. FDA is therefore retaining the original “medically plausible” terminology at § 316.25(a).

(Comment 2) Many comments asked FDA to clarify what subsets may be appropriate for the purpose of orphan-drug designation.

(Response) FDA advises sponsors that an orphan subset cannot be considered without reference to the drug, specifically to the property or properties of the drug that preclude its use in the remaining persons with the non-rare disease or condition, outside of the orphan subset. FDA explained in the proposed rule (76 FR 64868 at 64869 to 64870) what factors may inform whether an appropriate orphan subset exists for the purpose of orphan-drug designation. In response to these comments, FDA is providing further explanation here.

Factors that may inform whether an appropriate orphan subset exists

³ As in the proposed rule, in this final rule FDA is not changing the 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)).

include pharmacologic or biopharmaceutical properties of the drug and previous clinical experience with the drug. For example:

- **Toxicity of the Drug:** The toxicity profile of the drug may render it appropriate for use in only a subset of persons with a non-rare disease or condition. For example, patients with the disease or condition who can be treated with other, less toxic therapies may not be appropriate candidates for the drug; however, a subset of patients with the disease or condition who are refractory to, or intolerant of, other less toxic drugs may exist and may be the only appropriate candidates for treatment with the more toxic drug.

- **Mechanism of Action of the Drug (e.g., antibody-specific or biomarker-based drug):** The mechanism of action of a drug may limit use of a drug to only a subset of patients with a non-rare disease or condition. For example, use of a certain targeted therapy (e.g., antibody-specific or biomarker-based drug) may be appropriate in only a subset of patients with a non-rare disease or condition owing to its targeting mechanism (e.g., only in patients with the subtypes of tumors that possess the specific antigen targeted or only those patients with the specific biomarker targeted).

- **Previous Clinical Experience With the Drug:** Information on the drug's activity available from completed clinical trials or published in clinical literature may be used to establish an orphan subset. For example, if relevant data show that the drug has no significant activity in the remaining subset of patients with high grade tumors or with a certain biomarker, respectively, then patients with low grade tumors or without that biomarker may constitute an orphan subset within a given disease or condition.

Factors that may not inform whether an orphan subset exists were also addressed in the proposed rule (76 FR 64868 at 64869 to 64870). These factors may include, by way of example:

- **Clinical Trial Eligibility:** An orphan subset is not appropriate where the subset of interest is defined only by eligibility to enroll in a given clinical trial to support a specific indication for use of a drug, where other persons with the disease or condition may also be appropriate candidates for the drug. That is, patients with a given disease or condition who simply meet inclusion or exclusion criteria for a trial do not automatically qualify as an orphan subset absent some property(ies) of the drug that would render its use inappropriate in the remaining persons with the disease or condition.

- **Sponsor's Plan to Study the Drug for a Select Indication:** An orphan subset does not exist simply because the sponsor plans to study the drug for a select indication within a disease or condition absent some property(ies) of the drug that would render its use inappropriate in the remaining persons with the disease or condition.

- **Particular Disease Grade or Stage:** An orphan subset does not exist for a drug for use in a subset of persons with a particular pathohistologic grade or clinical stage of a specific malignancy absent some property(ies) of the drug that would render its use inappropriate in the remaining persons with the disease or condition.

- **Price:** An orphan subset does not exist simply because the high price of a drug may render it unlikely to be used in a broader population with the disease or condition. The sponsor must show that use of the drug in the remaining persons with the disease or condition would be scientifically or medically inappropriate, not simply unlikely because of price or other factors.

(Comment 3) Many of the comments expressed concern that, in order to establish an orphan subset, sponsors would have to prove a negative: That the drug would not potentially benefit other subsets of persons with the non-rare disease or condition. As one comment noted, "There may be reason to encourage study of a treatment for a clinically distinct subgroup, even if that treatment could also be used to treat a different clinically distinct subgroup or even a larger group with the same disease."

(Response) FDA understands the concern about "proof of a negative," but advises sponsors that an orphan subset cannot be artificially narrow. As noted in response to comments 1 and 2, an orphan subset must be based on some property(ies) of the drug, such as toxicity or mechanism of action, that would render its use inappropriate in the remaining persons with the disease or condition. This showing is not necessarily "proof of a negative," as these comments may suggest; it need not necessarily rise to the level of "scientific proof" as that term is commonly understood.

Some of the concerns expressed by these comments are best addressed through discussion of what constitutes a distinct "disease or condition" for the purpose of orphan-drug designation. A drug that shows promise in multiple, different rare diseases or conditions may be eligible for multiple designations, one for each disease or condition, because FDA considers the prevalence within each disease or condition. For

example, the same drug may be eligible for three separate designations: One for the treatment of ovarian cancer, one for the treatment of multiple myeloma, and one for the treatment of Kaposi's sarcoma, even if the cumulative prevalence of all three diseases or conditions would exceed 200,000. As long as the prevalence of each disease or condition is under 200,000, no orphan subset need be shown. If, however, the drug is for a disease or condition that exceeds the prevalence limit of 200,000, then the sponsor would need to establish an orphan subset based on some property(ies) of the drug, as described previously in the responses to comments 1 and 2.

Whether a given medical condition constitutes a distinct "disease or condition" for the purpose of orphan-drug designation depends on a number of factors, assessed cumulatively, including: Pathogenesis of the disease or condition; course of the disease or condition; prognosis of the disease or condition; and resistance to treatment. These factors are analyzed in the context of the specific drug for which designation is requested. For example, based on a cumulative assessment of the previous factors, FDA currently considers pneumonia in cystic fibrosis patients to be a different "disease or condition" than community-acquired pneumonia when evaluating orphan-drug designation requests for products that treat respiratory infection. Thus, assuming the prevalence of pneumonia in cystic fibrosis patients in the United States is under 200,000, but the pool of all pneumonia cases exceeds 200,000, sponsors seeking orphan-drug designation for a drug for pneumonia in cystic fibrosis patients need not establish an orphan subset from the larger pool of all pneumonia patients. They need not, in other words, provide a rationale for why only cystic fibrosis patients with pneumonia (and not patients with community-acquired pneumonia) would be appropriate candidates for the drug. By contrast, FDA currently considers stage 1 breast cancer to be the same "disease or condition" as stage 4 breast cancer when evaluating orphan-drug designation requests for products that treat breast cancer. Because the prevalence of breast cancer currently exceeds 200,000, sponsors seeking orphan-drug designation for a breast cancer drug would need to demonstrate why only a subset of patients with breast cancer (e.g., patients with stage 4 breast cancer) would be appropriate candidates for the drug. FDA acknowledges that what is considered a

distinct “disease or condition” may change over time as scientific understanding evolves, which would affect prevalence determinations.

If FDA considers the disease or condition in question to be a distinct “disease or condition” for the purpose of orphan-drug designation, then drugs for that disease or condition may be eligible for orphan-drug designation even if they may potentially benefit other patient groups (e.g., drugs for pneumonia in cystic fibrosis patients may be eligible for designation even if they may potentially benefit patients with community-acquired pneumonia). Assuming prevalence of the relevant disease or condition is under 200,000, no orphan subset need be shown; sponsors would not need to justify limiting use of the drug to only that rare disease or condition. A drug could thus be eligible for multiple designations if it meets the applicable criteria for orphan-designation for multiple diseases or conditions, one disease or condition per designation.

(Comment 4) One comment noted that the European Medicines Agency (EMA) uses the term “medically plausible” in its orphan drug program, and advised FDA to consult with EMA before removing the term from FDA regulations.

(Response) FDA reminds sponsors that, although FDA is replacing the term “medically plausible” with a description of what constitutes an orphan subset, FDA is not changing its longstanding approach to identifying when appropriate subsets exist for the purpose of orphan-drug designation. FDA is aware that EMA uses the term “medically plausible” in evaluating whether medicinal products are eligible for orphan-drug designation in the European Union. FDA appreciates that harmonization with EMA, where feasible, benefits many stakeholders, and to that end has created with EMA a “Common Application” for orphan-drug designation. There are, however, differences in the statutory and regulatory criteria for, and regulatory benefits associated with, orphan-drug designation in the United States compared to the European Union. Absent a myriad of legislative changes, FDA and EMA cannot completely harmonize in their approaches to designation. FDA believes that any benefit to be gained by retaining the term “medically plausible” in its regulations purely because the EMA employs the term is outweighed by the confusion this term has engendered among sponsors seeking designation from FDA.

(Comment 5) Two comments agreed with the proposal to replace “medically plausible” with a description of orphan subset. One of these comments requested the following two clarifications from FDA: One, that orphan subsets can exist regardless of whether the drug may be used or investigated in other subsets of persons with the non-rare disease or condition, as long as there is a reasonable scientific or medical basis for use of the drug in the subset of interest; and two, that orphan subsets can be based on biomarkers and other facets of “personalized medicine” (e.g., antibody-specific treatments).

(Response) The responses to comments 1 to 3 also address these comments. Consistent with FDA’s longstanding approach, eligibility for orphan subsets rests on whether some property(ies) of the drug render its use inappropriate in the remaining persons with the disease or condition, outside of the subset of interest. FDA disagrees that an orphan subset can exist whenever there is a basis for using the drug in the subset of interest, regardless of whether the drug can also be used in the remaining persons with the disease or condition. FDA does, however, recognize that orphan subsets may be predicated on biomarker-based and other targeted treatments as a principle for limiting the use of a drug to only a subset of patients with a non-rare disease or condition (e.g., the subset with the specific biomarker targeted).

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

(Comment 6) Four comments were opposed to the proposal to delete the word “orphan” from the phrase “approved orphan drug” in §§ 316.3(b)(3), 316.20(a) and (b)(5), and the proposal to revise § 316.25(a)(3) to read “already approved drug for the same disease or condition” (in place of “[a drug] that already has orphan-drug exclusive approval for the same disease or condition”), on the ground that FDA should grant designation more liberally by never requiring a plausible hypothesis of clinical superiority at the designation stage, even if the drug is otherwise the same as a previously approved drug (whether or not such previously approved drug has orphan exclusive approval). These comments interpret section 526 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360bb) to mandate orphan-drug designation of any drug for a rare disease or condition, even those that are the same drug as a previously

approved drug, regardless of clinical superiority, as long as the designation request for the drug is submitted before submission of the marketing application. At the same time, these comments acknowledge that, in order for the drug to receive and/or break orphan exclusivity under section 527 of the FD&C Act (21 U.S.C. 360cc), clinical superiority would need to be demonstrated upon approval if the drug is otherwise the same as a previously approved drug for the same use or indication.

According to these comments, more liberal granting of orphan-drug designation without changing orphan-drug exclusivity requirements would further the intent of the Orphan Drug Act, by fostering development of rare disease treatments without undercutting the exclusivity incentive/protection. Specifically, more liberal orphan-drug designation—even if orphan-drug exclusivity is not even theoretically available—would expand the universe of rare disease treatments eligible for the benefits (other than exclusivity) associated with designation under the Orphan Drug Act: particularly, Federal tax credits for the cost of conducting human clinical testing and exemption from application user fees.⁴ These comments noted that the benefits associated with designation have expanded since passage of the Patient Protection and Affordable Care Act (ACA) in 2010 (Pub. L. 111–148), to include exemption from the annual pharmaceutical fee (excise tax) levied by ACA and exclusion from the 340B Drug Discount Program. According to these comments, Congress used orphan-drug designation as a “proxy” for protection of rare disease treatments in the ACA but without necessarily realizing that not all rare disease treatments are eligible for orphan-drug designation.

Two of these comments identify plasma protein therapies, in particular, as deprived of the benefits related to orphan-drug designation. Macromolecules are considered to be the “same drug” under the Orphan Drug regulations if they have the same principal molecular structure, despite some differences in structural features. If the “same drug” has already been approved for the same use, designation requires a plausible hypothesis of clinical superiority. As one of these comments explained, “This [framework] affects the plasma protein therapeutics industry significantly because various drugs within each therapeutic class of

⁴ This exemption from application user fees was enacted as part of the Prescription Drug User Fee Act of 1992, since reauthorized.

products are considered to have the same principal molecular structures and would not be considered different under the regulations without a showing of clinical superiority, despite the fact that each therapy is a unique, non-interchangeable biological product. This has important ramifications for the plasma industry because it has developed an exceptionally diverse selection of branded products within each therapeutic class, thus the industry's portfolio is predominantly composed of second-to-market products indicated to treat rare diseases, but not orphan designated." Because many plasma protein therapies lack orphan-drug designation, they are apparently ineligible for the legislative incentives for rare disease treatments enacted in other statutes, despite being indicated solely for rare diseases. According to comments, this outcome "contradicts the overall purpose of the [Orphan Drug Act]" by "threatening the industry's capacity to continue to explore rare disease therapies."

(Response) FDA appreciates this perspective from industry about the impact that obtaining—or not obtaining— orphan-drug designation under the Orphan Drug Act may have under other statutes unrelated to the Orphan Drug Act. Nevertheless, FDA continues to believe that the current framework is the best means for giving effect to the intent of the Orphan Drug Act, to provide incentives for sponsors to develop promising drugs for rare diseases and conditions that would not otherwise be developed and approved, including drugs that are potentially safer or more effective than already approved drugs. (See H.R. Rep. 97–840, Pt. 1, at 6 (1982); Orphan Drug Act, Pub. L. 97–414, § 1; see also *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 312 (D.D.C. 1987) ("The legislative history is replete with references to the fundamental need to provide treatment for *presently untreated patients*.")) (emphasis added).

FDA is, however, considering the feasibility of issuing a draft guidance document on what may constitute a plausible hypothesis of clinical superiority for certain categories of products, for example plasma-derived products, which may help address some of the concerns articulated previously.

(Comment 7) One comment opposed this proposal as an apparent "expansion" of the circumstances in which FDA would require a plausible hypothesis of clinical superiority, rather than a clarification of existing practice. This comment maintained that any clinical superiority requirement undermines the incentive structure of

the Orphan Drug Act because clinical superiority can be difficult to prove.

(Response) As explained in the proposed rule (76 FR 64868 at 64870), FDA is not expanding the circumstances in which it will require a plausible hypothesis of clinical superiority for orphan-drug designation. It is merely clarifying its longstanding practice. In the absence of a clinical superiority hypothesis, the Agency does not interpret the Orphan Drug regulations to permit designation of a drug that is otherwise the same as a drug that is already approved for the same use, regardless of whether the previously approved drug obtained orphan-drug designation or was eligible for orphan-drug exclusivity. For a more detailed description of how FDA interprets its current regulations, see the response to comment 8. FDA believes this interpretation best reflects the intent of Orphan Drug Act, as explained in response to comment 6, by encouraging the development of potentially safer and more effective orphan drugs—rather than encouraging minor modifications to already approved drugs that confer no meaningful benefit to patients.

In response to the comment that clinical superiority can be difficult to prove, FDA advises sponsors that the clinical superiority requirements for orphan-drug designation and orphan-drug exclusivity are different: designation requires a plausible hypothesis of clinical superiority, exclusivity requires a demonstration of clinical superiority. As FDA has elsewhere explained (56 FR 3338 at 3341, January 29, 1991), this difference is intended to encourage the development of improved versions of existing drugs while protecting any applicable orphan-drug exclusivity. The former is achieved through liberally granting designation based on a plausible hypothesis of clinical superiority, allowing drugs to benefit from development incentives that flow from designation. The latter is achieved through reserving orphan-drug exclusivity for a subsequent drug—allowing the subsequent drug to be approved during the pendency of the already approved drug's exclusivity period (if any) and with its own period of orphan-drug exclusivity—provided that clinical superiority is demonstrated upon approval. This framework fulfills the main purpose of the Orphan Drug Act, to foster the development and innovation of orphan drug therapies, while taking care not to "render [orphan-drug exclusivity] meaningless" (57 FR 62077, December 29, 1992) e.g., by allowing any minor change to render a subsequent drug different from a

previously approved drug and therefore not blocked by orphan-drug exclusivity. At the same time, if the sponsor of a subsequent drug that it is otherwise the same as a previously approved drug demonstrates clinical superiority to the previously approved drug, that subsequent drug may gain marketing approval and its own orphan-drug exclusivity, despite any existing exclusivity for the previously approved drug; it would also be eligible for exclusivity upon a clinical superiority showing where the previously approved drug's exclusivity period has run or never existed. FDA has implemented the Orphan Drug Act in this way to fulfill Congress' aim of incentivizing the development and innovation of orphan drugs and to ensure that orphan exclusivity has value to sponsors, while limiting its scope so that it does not "preclude significant improvements in treating rare diseases" (56 FR 3338).

(Comment 8) One comment objected to FDA's characterizing this proposal as "clarifying current practice" on the ground that FDA appears to be contradicting its current regulations. According to this comment, current § 316.25 lists the only reasons that FDA can ever decline to grant a designation request—and § 316.25 does not expressly list, as a reason, failure to include a plausible hypothesis of clinical superiority where the drug is the same as a previously approved drug that does not have orphan-drug exclusivity.

(Response) FDA disagrees that it is changing its current practice. As FDA explained in the proposed rule (76 FR 64868 at 64870), FDA has consistently interpreted the Orphan Drug regulations (in particular, § 316.20(a) and (b)(5)) to require that designation requests include a plausible hypothesis of clinical superiority if the drug is the same as an already approved drug, regardless of whether the already approved drug has orphan-drug exclusivity. If the same drug has already been approved for the same use, with or without orphan-drug exclusivity, designation without such a hypothesis 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 orphan drugs that would not otherwise be developed and approved—not to encourage minor modifications to already approved drugs that confer no meaningful benefit to patients. See H.R. Rep. 97–840, Pt. 1, at 6 (1982); Orphan Drug Act, Public Law 97–414, § 1; see also *Genentech, Inc. v. Bowen*, 676 F. Supp. at 312 ("The legislative history is replete with references to the

fundamental need to provide treatment for *presently untreated patients.*”) (emphasis added).

FDA has never interpreted § 316.25, in particular, as an exhaustive list of the reasons that FDA can decline to grant designation. Although § 316.25 lists some reasons for refusing designation, it does not reiterate all of the eligibility criteria for designation that are embodied elsewhere in the statute and in part 316. These eligibility criteria include that the designation request be submitted before submission of the marketing application, as is required by section 526(a) and § 316.23(a), and that the product be a drug, as is required by section 526(a) and § 316.20. Under FDA’s longstanding interpretation, a request that failed to meet any of these eligibility criteria would be denied on this ground alone without resort to § 316.25. An additional reason for not granting designation that is not currently listed at § 316.25, but is reflected elsewhere in part 316 (§ 316.20(a) and (b)(5)), is if a request for a drug is the same as a previously approved drug fails to include a plausible hypothesis of clinical superiority where the previously approved drug does not have orphan-drug exclusivity. Consistent with the proposed rule, FDA is revising § 316.25 in this final rule to expressly include this reason in the enumerated list.

Similarly, FDA has never interpreted § 316.24 to require automatic designation if a product fails to meet eligibility criteria captured elsewhere in part 316 but not reiterated in § 316.25. If a request is not eligible for designation because, for example, it fails to include a plausible hypothesis of clinical superiority when the drug is the same as a previously approved drug, or because the designation request was submitted after the marketing application had been submitted, then the request would not even fall into the ambit of § 316.24 (“Granting orphan-drug designation”).

In response to this comment’s assertion that § 316.25 on its face appears to be an exhaustive list of the reasons that FDA can refuse to grant designation (especially when read alongside § 316.24), FDA has decided to further amend § 316.25(b) to make clear that FDA will deny designation if the request is otherwise ineligible for designation under part 316.

(Comment 9) One comment questioned why the preamble to the proposed rule identified change in dosage form as an example of “inappropriate ‘evergreening’ of exclusive approval periods” (76 FR 64868 at 64870), when some new dosage

forms may provide significant patient benefit.

(Response) FDA agrees with this comment. Some new dosage forms may be “clinically superior” to previously approved dosage forms of the same drug under § 316.3(b)(3) and thus eligible for their own 7-year period of orphan exclusive approval. For example, a change in delivery system from intravenous (IV) to oral may, in some cases and for some drugs, constitute a “major contribution to patient care” under § 316.3(b)(3)(iii). As stated in the preamble to the 1992 final rule, Orphan Drug Regulations (57 FR 62077 at 62079), whether a change in delivery systems constitutes a major contribution to patient care “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.” For more on major contribution to patient care, see the responses to comments 14 and 15.

(Comment 10) One comment asked FDA to clarify that a sponsor that improves its own drug by demonstrating patient benefit is eligible for orphan-drug exclusivity for the improved drug, regardless of whether the sponsor’s first drug received orphan-drug exclusivity.

(Response) FDA advises that if, upon approval, an orphan-designated drug is shown to be “clinically superior” under § 316.3(b)(3) to a previously approved drug, then it is eligible for orphan-drug exclusive approval regardless of the identity of the sponsor (e.g., even if the sponsor of both drugs is the same).

C. Eligibility for Multiple Orphan-Drug Exclusive Approvals

(Comment 11) One comment expressed confusion about the language in the preamble to the proposed rule (76 FR 64868 at 64870), “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.” The comment asked FDA to ensure that it would give orphan exclusive approval only to drugs that have been formally designated as orphan drugs, rather than

giving orphan exclusive approval to drugs for indications for which they do not have orphan-drug designation.

(Response) FDA clarifies that the language excerpted previously from the preamble to the proposed rule was intended to convey the following circumstance: (1) A drug obtains orphan-drug designation for a rare disease or condition, (2) a drug obtains marketing approval (and orphan-drug exclusivity) for only select indications or uses within the rare disease or condition for which the drug was designated, (3) the sponsor subsequently obtains approval for additional (not previously approved) indications or uses of the drug within the same rare disease or condition for which the drug was designated, then (4) the drug may be eligible for a new period of orphan-drug exclusivity for those new approved indications or uses without the need to re-seek designation—because these new (not previously approved) indications or uses would fall within the scope of the original designation (i.e., because in this example the drug was designated for the rare disease or condition, not select indications or uses within that rare disease or condition). This example was not intended to suggest that FDA would grant orphan exclusive approval to a drug for a disease or condition for which the drug was not designated.

FDA reminds sponsors that, when FDA designates an orphan drug, it generally designates the drug for use by all persons with the rare disease or condition (or the orphan subset within a non-rare disease or condition) and expects that a sponsor will seek marketing approval of the drug for all persons with the rare disease or condition (or the orphan subset). FDA may, however, approve the drug for only select indications or uses within the rare disease or condition (or the orphan subset) because FDA can only approve a drug for the indications or uses for which there is adequate data and information in the marketing application to support approval. The scope of orphan-drug exclusivity is limited to the indication(s) or use(s) for which the drug is approved for marketing, even if the orphan-drug designation for the drug is broader. For example, a drug may be designated for use in ovarian cancer but approved for use in only stage 4 ovarian cancer, based on the data and information in the marketing application. As new data emerge, FDA may approve the drug for additional indications or uses within the rare disease or condition for which the drug is designated (e.g., stages 1, 2, and/or 3 of ovarian cancer). The advantage to the sponsor in this

hypothetical scenario is that, if the drug is later approved for additional indication(s) or use(s) within the rare disease or condition for which it is designated, the sponsor would not have to submit additional designation requests for the drug to cover these additional indication(s) or use(s)—because they would fall within the original designation. Additional orphan-drug exclusivity may attach upon approval of these new (not previously approved) indications or uses that are within the scope of the original designation.

In such a hypothetical scenario, a “broad” designation would not prevent other sponsors from obtaining designation and/or marketing approval for the same drug for the same rare disease or condition. If a drug is approved for only certain indications or uses within a rare disease or condition, a subsequent sponsor may obtain designation of the same drug for the remaining (not previously approved) indications or uses within the same rare disease or condition without having to provide a plausible hypothesis of clinical superiority over the already approved drug, provided that the prevalence of the entire disease or condition remains under 200,000. Assume, for example, that a drug is designated for use in ovarian cancer (all stages) but is approved for use in only stages 1 and 2 of ovarian cancer (“first drug”). A subsequent sponsor may seek designation of the same drug (“second drug”) for the remaining unapproved uses within ovarian cancer (i.e., stages 3 and/or 4) without having to provide a plausible hypothesis of clinical superiority over the first drug, although the prevalence determination would be based on ovarian cancer regardless of stage (unless an orphan subset were shown). Designation of the second drug for the uses already approved for the first drug (i.e., stages 1 and 2 of ovarian cancer) would require a plausible hypothesis of clinical superiority over the first already approved drug.

Prompted by the confusion expressed by comment 11, FDA has revised proposed § 316.31 for clarity. FDA has amended the final rule by replacing “subset [of uses]” (i.e., a drug is approved for only a subset of patients with the rare disease or condition for which the drug is designated) with “select indication(s) or use(s),” at § 316.31(a) and (b). The rule now uses the phrase “indication(s) or use(s)” in place of “subset [of uses]” because readers may have confused the latter with the regulatory concept of orphan subset at § 316.20(b)(6)—when a reference to “orphan subset” was not

intended at § 316.31. Orphan subset is a regulatory concept relevant to eligibility for orphan-drug designation (see the responses to comments 1 to 3), whereas this regulation at § 316.31 concerns the scope of orphan-drug exclusive approval.

(Comment 12) One comment objected to FDA’s practice, described previously in response to comment 11, of generally designating a drug for use by all persons with the rare disease or condition, even though the drug may eventually be approved for only certain indication(s) or use(s) within that rare disease or condition. Once the drug has already been approved for certain indication(s) or use(s) within the rare disease or condition (“first drug”), another sponsor seeking designation of the same drug (“second drug”) for use in the same rare disease or condition would need to provide a plausible hypothesis of clinical superiority over the first drug for the indication(s) or use(s) for which the first drug is approved. Alternatively, without providing such a hypothesis, the sponsor may seek designation of the second drug for only the unapproved indication(s) or use(s) within the rare disease or condition. The comment maintained that this designation practice could result in labeling confusion, Medicare reimbursement confusion, increased likelihood of medication errors, and product liability concerns, because end-users may have difficulty differentiating between the trade names and labeling of orphan-designated drugs that are approved for different uses within the same rare disease or condition.

(Response) FDA advises that the concerns expressed by this comment mainly concern the wording and scope of FDA-approved labeling, not orphan-drug designation. Requests for orphan-drug designation are submitted before the submission of a marketing application for a drug; whatever the scope of a drug’s designation, its FDA-approved labeling will be determined by the data and information included in the marketing application. The scope of designation, in other words, does not determine the scope of FDA-approved labeling. As for the comment’s concern that several drugs that are the same may be approved for different indications or uses within the same rare disease or condition, as the 4th Circuit Court of Appeals has held, orphan-drug exclusivity protects only the uses for which the drug is approved, not any and all uses of the drug. See *Sigma-Tau Pharms. v. Schwetz*, 288 F.3d 141, 145 (2002).

(Comment 13) Another comment asked FDA to clarify that, in the event

a drug is designated for a given disease or condition, is approved (and granted orphan-drug exclusivity) for only certain indications or uses within that same disease or condition, and is subsequently approved for additional indications or uses within that same disease or condition, the drug is eligible for orphan-drug exclusivity without the need to show clinical superiority.

(Response) FDA agrees that, in the example provided previously, orphan-drug exclusivity may be obtained for the new indications or uses of the drug within the same disease or condition for which the drug was designated without the need to show clinical superiority, provided that the same drug has not already been approved for these new indications or uses. For more explanation, see the response to comment 11.

D. Demonstration of Clinical Superiority—Major Contribution to Patient Care

(Comment 14) Five comments asked FDA to clarify what “comparable safety and effectiveness” would mean in the context of major contribution to patient care under § 316.3(b)(3)(iii), and in particular what level of proof would be required (e.g., non-inferiority trials).

(Response) In response to these comments, FDA is deleting the “safety and effectiveness comparable to the approved drug” language from the final rule because of the confusion this language engendered. FDA did not intend to propose a new standard for major contribution to patient care with this language; in particular, FDA did not mean to suggest that direct proof of comparability to the already approved drug would be required (e.g., through non-inferiority trials). Instead, FDA intended to convey that major contribution to patient care determinations can be complex and encompass consideration of a number of factors that potentially implicate safety and effectiveness, which are evaluated on a case-by-case basis for each drug product. For more discussion of major contribution to patient care, see the responses to comments 9 and 15.

(Comment 15) Several comments asked for clarification of the meaning of “major contribution to patient care.” In particular, these comments asked FDA to reiterate and expand the list of factors that FDA had included in the preamble to the 1992 final rule, Orphan Drug Regulations (57 FR 62077 at 62079). The comments proposed the following additional factors: increased quality of life, reduced treatment burden, and improved patient compliance.

(Response) The following factors, when applicable to severe or life-threatening diseases, may in appropriate cases be taken into consideration when determining whether a drug makes a major contribution to patient care: convenient treatment location; duration of treatment; patient comfort; reduced treatment burden; advances in ease and comfort of drug administration; longer periods between doses; and potential for self-administration. FDA declines to add “increased quality of life” to this list because many factors already on the list may be viewed as increasing quality of life, such as increased patient comfort and longer periods between doses. FDA also declines to add “improved patient compliance” to the list of factors potentially informing whether a drug provides a major contribution to patient care, because FDA would expect improved patient compliance to be reflected in other factors already on this list (e.g., increased patient comfort, reduced treatment burden, etc.), if not otherwise reflected in greater safety or greater effectiveness showings for the drug. For more on major contribution to patient care, see the responses to comments 9 and 14.

(Comment 16) One comment asked FDA to delete the opening clause, “in unusual cases,” because major contribution to care findings should be more customary in light of recent protein engineering and extended release technologies, which allow for significant improvements in patient care.

(Response) In FDA’s experience, showings of major contribution to patient care remain unusual. Although new technologies may increase the number of drugs found to make such major contributions, FDA still expects these showings to be less frequent than greater safety and greater effectiveness showings. FDA is therefore retaining the clause, “in unusual cases.”

E. Name of the Drug

(Comment 17) One comment objected to the requirement to include a chemical name in the designation request at § 316.20(b)(4), if neither a generic nor trade name is available. Disclosing the chemical name (especially pre-patent) may put sensitive commercial information at risk, which could “negatively impact the potential to secure intellectual property rights and thus reduce the incentives for further development.”

(Response) FDA advises that sponsors need not include a chemical name in the designation request as long as they include a meaningful descriptive name of the drug. The final rule, like the

proposed rule, is phrased in the disjunctive: “the chemical name or a meaningful descriptive name of the drug” (emphasis added), if neither a generic nor trade name is available. By meaningful descriptive name, we mean a name that would be meaningful to the public. It could include information about the product class or type, the mechanism of action, how or where the product was derived, and other information as appropriate. An example of a meaningful descriptive name could be murine anti-CD30 monoclonal antibody, which describes the deoxyribonucleic acid (DNA) source, the cell being targeted by the product, and the product type. As described in the proposed rule (76 FR 64868 at 64872 to 64873), we do not consider internal business codes or other similar identifiers to be meaningful descriptive names.

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

(Comment 18) One comment asked that FDA add the qualifier “relevant” to modify “data” in the phrase “all data from in vitro laboratory studies” at § 316.20(b)(4).

(Response) FDA agrees and has amended the final rule accordingly.

(Comment 19) One comment asked why FDA would limit the clinical data to “clinical investigations of the drug in the rare disease or condition” when there may be pharmacokinetic (PK) or pharmacodynamic (PD) data in other conditions that are relevant to the proposed orphan use.

(Response) FDA advises that such PK and PD data are not generally relevant or necessary to an orphan drug designation request, and so FDA is not amending the proposed rule to require such data as suggested. Sponsors may, however, choose to provide such data if they believe such data are relevant or necessary to their request, for example, to provide a plausible hypothesis of clinical superiority over a previously approved drug.

On its own initiative, FDA has revised the regulatory language, “clinical investigations of the drug in the rare disease or condition,” for clarity. In this final rule, FDA has replaced “clinical investigations” with “clinical experience” to reflect that FDA may in some cases consider clinical data from sources other than clinical investigations, for example, from well-documented case histories or significant human experience with the drug, as appropriate. FDA will assess the relevance and significance of such data on a case-by-case basis.

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

(Comment 20) One comment asked FDA to clarify that having a designation request withdrawn or denied does not preclude re-submitting a request.

(Response) FDA agrees, although notes that eligibility for orphan-drug designation in terms of prevalence is evaluated at the time of the submission of the request (see § 316.21(b)). In the event a request is newly submitted after being withdrawn or denied, FDA will determine eligibility in terms of prevalence as of the date of the new submission. In response to this comment, FDA is considering whether to include language in its form letters to notify sponsors that they may submit a new request if their request is considered withdrawn or denied, but that eligibility in terms of prevalence will be evaluated at the time of any new submission.

Prompted by this comment, FDA has re-evaluated proposed § 316.24(a) for clarity and has made a ministerial edit. This edit makes clear that FDA will notify the sponsor whenever a request is considered voluntarily withdrawn, whether it is considered withdrawn because the sponsor failed to respond to a deficiency letter or request an extension of time to respond within 1 year, or because FDA denied the request for an extension of time. The language as proposed erroneously suggested that FDA would notify the sponsor in writing only in the latter instance.

H. Publication of Orphan-Drug Designations

(Comment 21) Five comments objected to possible disclosure by FDA of whether sponsors of designated drugs have submitted annual reports as required under § 316.30. In the preamble to the proposed rule (76 FR 64868 at 64873), FDA inquired whether such disclosure would help inform the public of the development status of orphan drugs. Many comments maintained that such information would likely create confusion and miscommunication, because failure to submit an annual report does not necessarily signal that the sponsor has ceased drug development. Many of these comments did, however, support broader disclosure of the development status of orphan drugs through means they considered more informative, such as: expanding the ClinicalTrials.gov database; devising and publishing an “inactive” status for orphan drug designations similar to the “inactive” status for Investigational New Drug

(IND) applications (see 21 CFR 312.42(g)); and publishing when drugs no longer have orphan-drug designation (e.g., because designation was voluntarily withdrawn by the sponsor). Some of these comments cautioned that any broader disclosure of orphan drug development status should be carefully tailored so as not to reveal highly sensitive commercial information that may violate legal protections and benefit only the sponsor's competitors, not patients with rare diseases.

(Response) FDA agrees that publishing whether or not sponsors have submitted annual reports as required under § 316.30 may not accurately inform the public as to the development status of orphan drugs. FDA has carefully considered the alternative disclosures suggested by the comments and has decided to adopt in this final rule one suggested approach: namely, to publish when drugs no longer have orphan-drug designation (either because the sponsor voluntarily withdrew designation or because FDA revoked designation under § 316.29).

FDA has amended § 316.28 to state that the publicly available cumulative posting of all drugs designated as orphan drugs, available on its Web site at <http://www.fda.gov/orphan/>, will include whether a drug no longer has designation and, if so, as of what date. The public was formerly able to deduce that a drug had lost designation from FDA's publication of hard copy quarterly lists of designated drugs: drugs no longer designated would appear on earlier hard copy lists but not on later ones. Once FDA switched to Internet publication, this information was no longer deducible owing to database limitations at the time. Once this rule takes effect, FDA will publish on the Internet a posting of drugs that, after the effective date of this rule, lose designation, but without specifying the reason (i.e., whether because the sponsor voluntarily withdrew designation or because FDA revoked designation under § 316.29). Publishing only the fact that a drug is no longer designated, and not also the underlying reason(s), mitigates any competitive concerns. Stakeholders may then choose to contact the sponsor for more information on the status of the drug's development. FDA advises sponsors that it will not publish when a designation request has been withdrawn; unlike designations, designation requests are generally not made public unless disclosed by the sponsor.

FDA has made conforming amendments to § 316.29 to reference this change to § 316.28. Relatedly, FDA

has added a § 316.24(d) to this final rule to make express an option that has always existed for sponsors—that they can voluntarily withdraw a designation request, or a designation proper, at any time by requesting such a withdrawal in writing from FDA. FDA will acknowledge such withdrawal in a letter to the sponsor. Any current or pending benefits attendant to designation, such as orphan-exclusive approval, will cease once designation is voluntarily withdrawn from the date of FDA's acknowledgement letter. The same holds true when FDA has revoked designation under § 316.29. See § 316.29(b). Any benefits that have already vested, such as tax credits or user fee exemptions, would not be affected.

FDA has determined that a reproposal to reflect these edits is neither necessary for reasoned decisionmaking nor desirable as a matter of policy. As noted previously, the proposed rule (76 FR 64868 at 64873) stated that FDA was “considering ways to make available to the public information about the status of development for designated orphan drugs” and invited comments on whether to provide this information to the public through disclosure of the submission status of annual reports. All comments that addressed this topic supported broader disclosure of some sort on the development status of orphan drugs, just not disclosure of the submission status of annual reports. Many of these comments specifically recommended publishing when a drug loses designation. This information used to be deducible from FDA's hard copy publication of quarterly lists of designated drugs; once FDA switched to Internet publication, this information was no longer deducible owing to database limitations at the time.

Finally, FDA has on its own initiative updated § 316.28 to reflect that, as of at least a decade ago, FDA no longer places an annual list of designated drugs on file at the FDA Division of Dockets Management. This is a technical amendment reflecting established practice.

(Comment 22) One comment advised FDA that the best way to achieve compliance with the annual reporting requirement is through one-on-one interaction with sponsors who do not submit annual reports as required under § 316.30.

(Response) FDA agrees with this comment.

(Comment 23) One comment asked FDA to make public its finding on the acceptability of specific prevalence data to reduce uncertainty about designation requirements. “This will allow sponsors

to use prevalence data already assessed by FDA and thereby streamline the process for obtaining these data to complete applications.”

(Response) FDA does not accept this suggestion. As explained in the preamble to the 1991 proposed rule, Orphan Drug Regulations, FDA believes that such an approach would unfairly allow subsequent sponsors to get a “free ride” in designation requests: “FDA believes it unfair to allow a subsequent sponsor to use a pioneer sponsor's research data for the purpose of obtaining orphan-drug designation when such research data would by law not otherwise be available to the subsequent sponsor” (56 FR 3338 at 3340). Further, prevalence data are often specific to each designation request in terms of both the timing of the request and the properties of the drug for which the request is submitted. Under § 316.21(b), eligibility in terms of prevalence is determined at the time of the submission of the request. Under § 316.20(b)(6), the prevalence estimate may be narrowed owing to one or more properties of the drug that allow for the existence of an orphan subset (i.e., only a subset of persons with the disease or condition would be appropriate candidates for use of the drug). These two factors make prevalence determinations specific to each request and further counsel against FDA publicly disclosing prevalence data and the acceptability thereof.

(Comment 24) Two comments asked FDA to revise its publicly available posting of orphan designated drugs to include additional information. One of these comments asked that the posting include all designated biological products approved via a Biologics License Application (BLA) and granted orphan-drug exclusivity, along with the dates of grant and expiry; the other comment asked FDA to highlight when a designated drug is approved for the orphan use but does not receive orphan-drug exclusivity.

(Response) FDA advises that its current publicly available posting of orphan designated drugs, available on its Web site at <http://www.fda.gov/orphan/>, includes biological drug products licensed via BLA, in addition to drug products approved via a New Drug Application (NDA). FDA is in the process of adding to this database reference to any applicable orphan-drug exclusivity periods. Once this revision to the database is complete, the absence of such information may possibly indicate that the product did not receive orphan-drug exclusivity upon approval (or alternatively that the information has not yet been entered into the database).

Stakeholders may also contact sponsors directly for the information and, for drugs approved via NDA, review the FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book), available electronically at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

FDA is making a ministerial edit to § 316.34(b) in response to this comment, to clarify that the Orange Book includes only information about products approved under section 505 of the FD&C Act (21 U.S.C. 355). FDA is also adding an online address for the Orange Book.

I. FDA Recognition of Orphan-Drug Exclusive Approval

(Comment 25) Two comments objected to FDA approving an orphan-designated drug but withholding orphan-drug exclusivity, for example, if the drug is the same as a previously approved drug and clinical superiority is not demonstrated upon marketing approval. These comments contended that, under section 527 of the FD&C Act, orphan-drug exclusivity should automatically attach once a designated drug is approved for the rare disease or condition for which it was designated, whether or not it is the first drug to be approved for this use. One of these comments characterized FDA regulations at §§ 316.31(a) and 316.34(a) as apparently confirming this “automatic award” of exclusivity upon approval of any designated drug.

(Response) FDA disagrees. FDA has long interpreted the Orphan Drug Act to accord orphan exclusive approval only to the first drug approved for the disease or condition (see 56 FR 3338 at 3341). The statute cannot be logically read to confer exclusivity to every designated drug that gets approved, as these comments suggest.

Section 527 generally confers exclusivity by prohibiting FDA from approving later drugs after a previous drug has been designated and approved. “[I]f the Secretary [] approves an application . . . for a drug designated under section 526 . . . the Secretary may not approve another application . . . for such drug . . . until the expiration of seven years from the date of the approval of the approved application.” Section 527(a) (emphasis added). Courts construing this statute have held “such drug” to be ambiguous; they have further upheld FDA’s regulatory scheme to require a showing of clinical superiority over a previously approved drug in order for the clinically superior drug to not be blocked by another sponsor’s exclusivity and to be eligible for its own period of exclusivity.

See, e.g., *Baker Norton Pharms. v. FDA*, 132 F. Supp. 2d 30, 37 (D.D.C. 2001).

Section 527 is also ambiguous on the question of whether a drug may be eligible for exclusivity when another drug that is the same has already been approved for the same use. See section 527(a) (referring to an approved drug and unapproved applications for such drug, but not to any drugs approved previously to the approved drug). Under FDA’s longstanding interpretation, any such previously approved drug precludes exclusivity absent a showing of clinical superiority because sponsors could otherwise: (1) Obtain infinite, successive 7-year periods of exclusivity for the same drug for the same use when the previously approved drug had such exclusivity, known as “evergreening,” or (2) obtain an exclusivity period for a drug without providing any meaningful benefit to patients over previously approved therapies, when the previously approved drug did not have orphan exclusivity. Both results would be at odds with the Orphan Drug Act.

“Evergreening” would allow orphan exclusivity to be extended indefinitely for the same drug for the same use without any meaningful benefit to patients, a result at odds with the 7-year exclusivity period provided by the statute. See *Baker*, 132 F. Supp. at 37 (noting with approval that, under FDA’s interpretation, “market exclusivity rights are limited in time to seven years, and granted only for a particular drug for a particular use”). Congress would not have prescribed a definite period of exclusivity and at the same time provided for means to indefinitely extend that period. Indeed, the legislative history reflects this by stating that even if multiple sponsors get designation for the same drug, “only the first sponsor to be approved is awarded the seven year market exclusivity for that drug for the approved use.” H.R. Rep. 100–473, at 6 (1987). Further, where the first approved drug does not have orphan designation or exclusivity, awarding orphan exclusivity to a second-in-time drug that has not been shown to be clinically superior to the first approved drug—as these comments suggest doing—would be incompatible with the core objective of the Orphan Drug Act, to encourage development of drugs that would not otherwise be developed and approved (not to encourage minor modifications to already approved drugs that confer no meaningful benefit to patients). See H.R. Rep. 97–840, Pt. 1, at 6 (1982); 56 FR 3338; *Genentech*, 676 F. Supp. at 305–06, 312.

FDA’s longstanding interpretation of section 527—to accord orphan exclusive

approval only to the first approved drug for the disease or condition (assuming it has been designated)—implements the exclusivity period as written, is consistent with FDA’s regulatory framework, and best effectuates Congress’ aim in enacting the Orphan Drug Act. FDA’s interpretation is also consistent with the decisions of courts that have had occasion to address orphan exclusivity. See *Genentech*, 676 F. Supp. at 304 (orphan exclusivity “is reserved for the first manufacturer to receive full FDA approval of its drug as safe and effective for commercial sale,” even if multiple drugs have orphan designation); cf. *Baker*, 132 F. Supp. 2d at 31 (if two drugs are the same under FDA regulations, “the second drug may not be approved for market exclusivity”).

Accordingly, FDA is retaining § 316.34(c) in this final rule to make clear that a designated drug will receive orphan-drug exclusivity upon approval only if the same drug has not been previously approved for the same orphan use: that is, if the drug is otherwise the same as a previously approved drug, it will receive exclusivity only upon a demonstration of clinical superiority. FDA is, however, amending the final rule slightly so that it reads: “If a drug is otherwise the same drug as a previously approved drug for the same use or indication, FDA will not recognize orphan-drug exclusive approval if the sponsor fails to demonstrate upon approval that the drug is clinically superior to the previously approved drug.”⁵ This revision clarifies for sponsors that, even if they obtained orphan-drug designation for a drug without having to provide a plausible hypothesis of clinical superiority (because the same drug was not yet approved for the same orphan use), they will have to demonstrate clinical superiority in order to obtain orphan-drug exclusivity if—in the interim between their obtaining orphan-drug designation and marketing approval for their drug—the same drug is approved for the same use.⁶ This longstanding interpretation gives best effect to the intent of the Orphan Drug Act, described previously.

This revision to § 316.34(c) also corrects a possible misunderstanding of the proposed rule. The proposed rule may have been read to suggest that, if a designation is based on a plausible hypothesis of clinical superiority, the

⁵ The term “upon approval” in this context does not preclude the possibility that clinical superiority may be demonstrated in a supplemental submission for the drug after approval.

⁶ FDA’s form letters granting orphan-drug designation alert sponsors to this possibility.

sponsor can obtain orphan-drug exclusivity only by substantiating the precise hypothesis upon which the designation was based (e.g., this drug is safer than the same previously approved drug because of the elimination of a certain ingredient). Rather, under FDA's interpretation, orphan-drug exclusivity would attach to a designated drug that is otherwise the same as a previously approved drug as long as it is shown to be clinically superior upon approval, whether or not the showing of clinical superiority at the approval stage aligns with the plausible hypothesis of clinical superiority provided at the designation stage (e.g., if the drug is shown to be safer for a different reason or is instead shown to be more effective). FDA understands that a hypothesis of clinical superiority (required for orphan-drug designation) is often devised early in the drug development process, and that subsequent research may result in enhanced understanding of the drug and possibly even changes to the drug itself. To not recognize orphan-drug exclusivity for a designated drug that is demonstrated to be clinically superior to a previously approved drug that is otherwise the same, solely because the sponsor inaccurately hypothesized the basis for clinical superiority, would contravene the intent of the Orphan Drug Act. Recognizing exclusivity in this instance encourages the development of safer and more effective orphan drugs.

Finally, in response to the assertion in this comment that §§ 316.31(a) and 316.34(a) apparently "confirm" that all designated drugs receive orphan-drug exclusivity upon approval (whether or not they are the first such drug approved), FDA has slightly revised §§ 316.3(b)(12), 316.31(a) and 316.34(a) to clarify that FDA recognizes orphan-drug exclusivity for the designated drug only if the same drug has not already been approved for the same use or indication. This revision clarifies FDA's longstanding interpretation of these provisions, as noted previously. Because this interpretation was explained in the preamble to the proposed rule (76 FR 64868 at 64870 to 64873), and reflected in the proposed rule at § 316.34(c), FDA has determined that a reproposal to amend §§ 316.3(b)(12), 316.31(a), and 316.34(a) in this manner is not required.

(Comment 26) One comment asked FDA to confirm that head-to-head safety trials may not always be necessary to establish clinical superiority based on greater safety, under § 316.3(b)(3)(ii).

(Response) FDA agrees. The regulation at § 316.3(b)(3)(ii) expressly states that direct comparative clinical trials to demonstrate greater safety may

be necessary in only "some cases." (By contrast, the regulation at § 316.3(b)(3)(i) states that direct comparative clinical trials to demonstrate greater effectiveness is necessary in "most cases.") Instead of prescribing the precise type and amount of evidence necessary for demonstrating "greater safety in a substantial portion of the target populations," the regulation at § 316.3(b)(3)(ii) allows FDA to determine on a case-by-case basis what type and amount of evidence suffice for a given drug.

J. Miscellaneous Comment

(Comment 27) One comment asked FDA to clarify when a sponsor may lose orphan-drug designation once the drug is in widespread use for the orphan indication.

(Response) A drug may be approved for multiples uses, some of which have orphan-drug designation and some of which do not. Simply because a drug is "in widespread use" does not mean that a sponsor will lose orphan-drug designation. A sponsor may lose designation if, for example, the drug was not in fact eligible for designation at the time the request was submitted or if the request contained an untrue statement of material fact. See § 316.29(a).

K. Initial Paperwork Burden Estimates

(Comment 27) One comment stated that FDA had underestimated the time it would take to prepare and submit each extension request under § 316.24(a), including time to develop and articulate a rationale for the requested extension and to obtain internal approval of the request before submission to FDA.

(Response) FDA has increased this estimate from 2 to 6 hours, as described in section VIII.

IV. 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.

V. Legal Authority

FDA is issuing this final 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, 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 section 527 of the FD&C Act and section 528 of the FD&C Act (21 U.S.C. 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. This final rule clarifies regulatory provisions in the 1992 final rule and makes minor improvements to address issues that have arisen since that rule took effect.

This final rule furthers 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, including potentially safer or more effective orphan drugs. It does so in several ways by:

- Enhancing clarity for sponsors in seeking orphan-drug designations and orphan-drug exclusive marketing approval;
- Making clear that the possibility of orphan-drug exclusivity remains for sponsors who develop a potentially promising drug for use by the remaining persons affected by a rare disease or condition after the same drug has been approved for only a portion of that population;
- Clarifying that orphan-drug exclusivity is given to a designated drug upon approval only if it is the first drug approved for the orphan use, thus encouraging innovation in rare disease treatments; and

- Helping ensure that the orphan-drug 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 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. This final rule helps the efficient enforcement of the Orphan Drug Act provisions by enhancing clarity and certainty in FDA's administration of the orphan drug program.

VI. Implementation Plan

These regulatory changes take effect 60 days after the date of publication of the final rule. The final rule applies only to original orphan-designation

requests submitted on or after the effective date of the final rule. It does not apply to: (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. The final rule has no effect on the scope of or eligibility for orphan-drug exclusive approval because it merely clarifies existing and longstanding FDA practice. Under this final rule, FDA will publicize if a drug no longer has designation only if the loss of designation occurs after the effective date of the rule (either because of voluntary withdrawal by the sponsor or because of revocation by FDA).

VII. Executive Order 13132: Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the final rule does 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 has concluded 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.

VIII. Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). A description of these requirements is provided in the paragraphs that follow with 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.

Title: Orphan Drug Regulations

Description: The rule finalizes revisions to the Orphan Drug regulations that clarify FDA policy and make minor improvements. The 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. For the initial PRA analysis, FDA estimated the annual reporting burdens for the two collections of information included in the proposed rule that were not already included in part 316 and already approved by OMB in accordance with the PRA (44 U.S.C. 3501–3520), under OMB control number 0910–0167. For this PRA analysis, FDA likewise estimates the annual reporting burdens for these two collections of information, which are being finalized as originally proposed.

One requirement is 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 will 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 new 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 requirement is 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 revision is necessary to ensure that deficient designation requests do not become “stale” by the time they are granted, such that the basis for the initial request may no longer hold (i.e., the prevalence of the disease or condition may now exceed 200,000). 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. This situation—where a request for designation languishes for a year or more before being granted—is distinct from situations where a designation request is granted but development of the drug languishes, whether for scientific, business, or other reasons.

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. In the initial PRA analysis, FDA estimated that it would 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. In response to one comment that 2 hours was an underestimate of the time required, FDA has increased this estimate to 6 hours to better account for the time needed to obtain internal approval of a 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	4
316.24(a)	10	1	6	60
Total Burden Hours	64

¹ There are no capital costs or operating and maintenance costs associated with this collection of information. Except with respect to the revisions addressed immediately previously, the revisions in this final rule merely 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 PRA (44 U.S.C. 3501–3520), under OMB control number 0910–0167.
 * 12 minutes.

In compliance with the PRA (44 U.S.C. 3407(d)), the Agency has submitted the information collection provisions of this final rule to OMB for review. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB’s decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

IX. Analysis of Impacts

FDA has examined the impacts of the 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 final 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 rule primarily clarifies current practice and any costs would be very small, the agency certifies 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 one year.” The current threshold after adjustment for inflation is \$139 million, using the most current (2011) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this 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 their subset analysis, and that problems with population subsets constituted over all half of the deficiencies, highlights the need to clarify existing regulatory language regarding subsets.

The confusion about regulatory language was not limited to issues regarding population subsets. Many designation requests were deficient because the submitted drug description was not adequate to establish whether the drug was the same as one that has already been approved. There were 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 lacked 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 final rule clarifies regulatory language to reduce sponsor and FDA costs and streamline the orphan-drug designation process.

B. Benefits and Costs of the Proposed Rule

This final rule reduces costs to sponsors who might otherwise submit deficient orphan-drug designation requests or face additional costs to determine program requirements. It benefits sponsors and promotes public health by clarifying requirements for sponsors who might otherwise be discouraged from submitting designation requests when their drug is in fact eligible for orphan-drug designation. The rule also reduces costs to FDA from responding to sponsor inquiries and deficient designation requests. There are small costs associated with the requirement that sponsors either respond to deficiency letters within a year or obtain an extension of time to respond.

We clarify what population or disease subsets may be eligible for orphan-drug designation (§ 316.3(b)(13) and § 316.20(b)(6)). This action merely clarifies longstanding policy and should reduce uncertainty about the requirements for orphan-drug designation, thus resulting in fewer requests that do not result in orphan-

drug designation. In addition, some sponsors may realize that their drug is not eligible for orphan-drug designation. Such sponsors would save the cost they would have otherwise incurred in submitting a request. FDA has recently (76 FR 3911) estimated a burden of 150 hours to complete a designation request. At a benefit-adjusted hourly wage of about \$46 for a regulatory affairs official, sponsors not submitting a request that cannot be granted would avoid \$6,900 in labor costs.⁷ Under this 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.

FDA's longstanding interpretation of the Orphan Drug Act and Orphan Drug regulations is that a designation request for a drug that is otherwise the same as a drug previously approved for the same use must include a plausible hypothesis of clinical superiority, regardless of whether the already approved drug received orphan-drug designation and exclusivity. FDA continues to receive requests that do not result in orphan-drug designation because this interpretation is not explicit in current regulation. This rule would make the regulatory language explicitly state FDA's interpretation, 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 select indications or uses within a rare disease or condition for which the drug is designated, FDA may grant orphan-drug designation and orphan-drug exclusive approval for use of the same drug in one or more of the remaining (not previously approved) indications or uses within the rare disease or condition without requiring any showing of clinical superiority. Current § 316.31 does not

explicitly mention this prospect, which could deter confused sponsors from pursuing designation for use of the drug in remaining indications or uses 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 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 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). Chemical and 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 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 rule clarifies 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 rule reduces sponsor and FDA costs.

We 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 clarifies 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 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-drug 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 benefits sponsors and public health by reducing the likelihood of a confused sponsor failing to seek orphan-drug designation for an eligible product.

We impose a 1-year time limit for sponsors to respond to deficiency letters or request a time extension (§ 316.24(a)). 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. 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 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. 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 6 hours of time from a regulatory affairs specialist. At a benefit-adjusted hourly wage of \$46, the cost to submit an extension request is \$276. Based on our

⁷ 2010 National Industry-Specific Occupational Employment and Wage Estimates, U.S. Department of Labor Statistics, last modified May 17, 2011 (www.bls.gov/oes/current/naics4_325400.htm); mean compliance officer wage rate of \$35.28 for pharmaceutical and medicine manufacturing (North American Industry Classification System (NAICS) 325400) plus a 30-percent increase for benefits.

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 \$2,760. 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.

We clarify that sponsors can voluntarily withdraw a designation request, or designation proper, at any time by submitting a written request to FDA (§ 316.24(d)). This is consistent with current practice and imposes no new costs on sponsors. Some sponsors are unaware of this option so this will save sponsors and FDA costs associated with unnecessary inquiries.

We clarify that FDA may refuse to grant a designation request if the request is otherwise ineligible for designation under part 316 (§ 316.25(b)). Because this change merely codifies existing practice, it is not expected to impose any new costs.

This rule provides that FDA will publish the fact a drug is no longer designated (§ 316.28(e)). Sponsors who may otherwise have been deterred from developing a drug because of another sponsor's designation of the drug may now seek their own designation for that drug and develop it upon learning that the first sponsor no longer has designation. The cost to FDA to publish this information is too small to reliably estimate.

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 for the same use fails to demonstrate clinical superiority upon approval. We make this policy explicit by adding proposed § 316.34(c). This clarification is applicable to only a very small portion of designated drugs

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 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 rule is an annual \$2,760, attributable to the submission of requests for additional time to respond to deficiency letters.

C. Small Business Analysis

This rule applies to the sponsors of orphan-drug designation requests. According to the Table of Small Business Size Standards, the U.S. Small Business Administration 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.⁸ 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 rule clarify regulatory language consistent with current practice, imposing no new costs. The 1-year time limit to respond to FDA deficiency letters would result in estimated costs of \$276 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 rule is approximately 1/33 of 1 percent of annual shipments for the smallest affected establishments, we conclude this rule does not constitute a significant impact on a substantial number of small entities.

List of Subjects in 21 CFR Part 316

Administrative practice and procedure, Investigations, Medical

⁸ 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

research, Drugs, 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 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), and (b)(12), by redesignating paragraphs (b)(13) and (b)(14) as paragraphs (b)(14) and (b)(15), respectively, and by adding a new paragraph (b)(13) 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

* * * * *

(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 or indication for 7 years, except as

otherwise provided by law or in this part. A designated drug will receive orphan-drug exclusive approval only if the same drug has not already been approved for the same use or indication.

(13) *Orphan subset of a non-rare disease or condition* (“orphan subset”) means that use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but use of the drug outside of that subset (in the remaining persons with the non-rare disease or condition) would be inappropriate owing to some property(ies) of the drug, for example, drug toxicity, mechanism of action, or previous clinical experience with the drug.

* * * * *

■ 4. Section 316.4 is revised to read as follows:

§ 316.4 Address for submissions.

All correspondence and requests for FDA action under the provisions of this rule should be addressed as follows: Office of Orphan Products Development, Food and Drug Administration, Bldg. 32, Rm. 5271, 10903 New Hampshire Ave., Silver Spring, MD 20993.

■ 5. Section 316.20 is amended by revising paragraphs (a), (b)(2), (b)(3), (b)(4), (b)(5), and (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, telephone

number, and email address; 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 relevant data from in vitro laboratory studies, preclinical efficacy studies conducted in an animal model for the human disease or condition, and clinical experience with 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 sponsor requests orphan-drug designation for a drug for only a subset of persons with a particular disease or condition that otherwise affects 200,000 or more people (“orphan subset”), 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 316.22 is revised to read as follows:

§ 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, address, telephone number, and email address shall be provided to: Office of Orphan Products Development, Food and Drug Administration, Bldg. 32, rm. 5271, 10903 New Hampshire Ave., Silver Spring, MD 20993.

■ 8. 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.

■ 9. Section 316.24 is amended by revising the section heading, redesignating paragraphs (a) and (b) as

paragraphs (b) and (c), respectively, and by adding new paragraphs (a) and (d) 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. In the event FDA considers a designation request voluntarily withdrawn, FDA will so notify the sponsor in writing.

* * * * *

(d) A sponsor may voluntarily withdraw an orphan-drug designation request or an orphan-drug designation at any time after the request is submitted or granted, respectively, by submitting a written request for withdrawal to FDA. FDA will acknowledge such withdrawal in a letter to the sponsor. Any benefits attendant to designation (such as orphan-exclusive approval) will cease once designation is voluntarily withdrawn, from the date of FDA's acknowledgement letter. If a sponsor voluntarily withdraws designation, FDA will publicize such withdrawal in accordance with § 316.28.

■ 10. Section 316.25 is amended by revising paragraphs (a)(1)(ii), (a)(3), and (b) 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.

(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 or if the request is otherwise ineligible under this part.

■ 11. 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.

■ 12. 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 posting of all drugs designated as orphan drugs. These postings 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;
- (d) The designated use in the rare disease or condition; and

(e) If the drug loses designation after August 12, 2013, the date of it no longer having designation.

■ 13. Section 316.29 is amended by adding a new paragraph (d) to read as follows:

§ 316.29 Revocation of orphan-drug designation.

* * * * *

(d) If FDA revokes orphan-drug designation, FDA will publicize that the drug is no longer designated in accordance with § 316.28(e).

■ 14. Section 316.31 is amended by revising the introductory text of paragraph (a), by redesignating paragraph (b) as paragraph (c), by revising newly redesignated paragraph (c), and by adding new paragraph (b) to read as follows:

§ 316.31 Scope of orphan-drug exclusive approval.

(a) FDA may approve a sponsor's marketing application for a designated orphan drug for use in the rare disease or condition for which the drug was designated, or for select indication(s) or use(s) within the rare disease or condition for which the drug was designated. Unless FDA previously approved the same drug for the same use or indication, FDA will not approve another sponsor's marketing application for the same drug for the same use or indication 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 approval is limited to only particular indication(s) or uses(s) within the rare disease or condition for which the drug was designated, FDA may later approve the drug for additional indication(s) or uses(s) within the rare disease or condition not protected by the exclusive approval. If the sponsor who obtains approval for these new indication(s) or uses(s) has orphan-drug designation for the drug for the rare disease or condition, FDA will recognize a new orphan-drug exclusive approval for these new (not previously approved) indication(s) or use(s) from the date of approval of the drug for such new indication(s) or use(s).

(c) 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 Federal Food, Drug, and Cosmetic Act until the expiration of

the period of exclusive marketing of another drug, FDA will so notify the sponsor in writing.

■ 15. Section 316.34 is revised to read as follows:

§ 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, if the same drug has not already been approved for the same use or indication. 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 under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) 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, and is also available online at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

(c) If a drug is otherwise the same drug as a previously approved drug for the same use or indication, FDA will not recognize orphan-drug exclusive approval if the sponsor fails to demonstrate upon approval that the drug is clinically superior to the previously approved drug.

■ 16. Section 316.50 is revised to read as follows:

§ 316.50 Guidance documents.

FDA's Office of Orphan Products Development will maintain and make publicly available a list of guidance documents that apply to the regulations in this part. The list is maintained on the Internet and is published annually in the **Federal Register**. A request for a copy of the list should be directed to the Office of Orphan Products Development, Food and Drug Administration, Bldg. 32, rm. 5271, 10903 New Hampshire Ave., Silver Spring, MD 20993.

Dated: June 7, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-13930 Filed 6-11-13; 8:45 am]

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DEPARTMENT OF HOMELAND SECURITY

Coast Guard

33 CFR Part 100

[Docket No. USCG-2013-0369]

RIN 1625-AA08

Special Local Regulation; Kelley's Island Swim, Lake Erie; Kelley's Island, Lakeside, OH

AGENCY: Coast Guard, DHS.

ACTION: Notice of enforcement of regulation.

SUMMARY: The Coast Guard will regulate vessel movement in portions of Lake Erie during the annual Kelley's Island Swim from. This special local regulated area is necessary to protect swimmers from vessel traffic.

DATES: The regulations in 33 CFR 100.921 will be enforced between 7 a.m. and 11 a.m. on July 10, 2013.

FOR FURTHER INFORMATION CONTACT: If you have questions on this notice, call or email MST2 Annaliese Ennis, Assistant Waterways Branch Chief, Marine Safety Unit Toledo, 420 Madison Ave., Suite 700, Toledo, OH 43604; telephone (419) 418-6041; email Annaliese.K.Ennis@uscg.mil.

SUPPLEMENTARY INFORMATION: The Coast Guard will enforce the special local regulations listed in 33 CFR 100.921 Special Local Regulation; Kelley's Island Swim, Lake Erie, Lakeside, OH, which was published in the December 3, 2012, issue of the **Federal Register** (77 FR 71531). These special local regulations will be enforced from 7 a.m. until 11 a.m. on July 10, 2013. Pursuant to 33 U.S.C. 1236 and 33 CFR 27.3, those who fail to comply with the special local regulations in 33 CFR 100.921 during this enforcement period will be subject to a civil penalty of up to \$8,000.

Under the provisions of 33 CFR 100.921, vessels transiting within the regulated area shall travel at a no-wake speed and remain vigilant for event participants and safety craft. Additionally, vessels shall yield right-of-way for event participants and event safety craft and shall follow directions given by the Coast Guard's on-scene representative or by event

representatives during the event. The "on-scene representative" of the Captain of the Port Detroit is any Coast Guard commissioned, warrant, or petty officer who has been designated by the Captain of the Port Detroit to act on his behalf. The on-scene representative of the Captain of the Port Detroit will be aboard either a Coast Guard or Coast Guard Auxiliary vessel. The Captain of the Port, Sector Detroit or his designated on scene representative may be contacted via VHF Channel 16.

This notice is issued under the authority of 33 CFR 100.921 and 5 U.S.C. 552(a).

Dated: May 28, 2013.

J. E. Ogden,

Captain, U.S. Coast Guard, Captain of the Port Detroit.

[FR Doc. 2013-13906 Filed 6-11-13; 8:45 am]

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DEPARTMENT OF HOMELAND SECURITY

Coast Guard

33 CFR Parts 100 and 165

[Docket No. USCG-2012-1057]

Special Local Regulations and Safety Zones; Recurring Events in Northern New England

AGENCY: Coast Guard, DHS.

ACTION: Notice of enforcement of regulations.

SUMMARY: The Coast Guard will enforce the events outlined in Tables 1 and 2 taking place throughout the Sector Northern New England Captain of the Port Zone. This action is necessary to protect marine traffic and spectators from the hazards associated with powerboat races, regattas, boat parades, rowing and paddling boat races, swim events, and fireworks displays. During the enforcement period, no person or vessel may enter the Special Local Regulation area or Safety Zone without permission of the Captain of the Port.

DATES: The marine events listed in 33 CFR 100.120 and 33 CFR 165.171 will take place during the times and dates specified in Tables 1 and 2 in

SUPPLEMENTARY INFORMATION.

FOR FURTHER INFORMATION CONTACT: If you have questions on this notice, call or email Ensign Elizabeth V. Morris, Waterways Management Division at Coast Guard Sector Northern New England, telephone 207-767-0398, email Elizabeth.V.Morris@uscg.mil.

SUPPLEMENTARY INFORMATION: The Coast Guard will enforce the Special Local