Orphan Drug Regulations: Proposed rule

RIN 0910-AG72

SUPPORTING STATEMENT

Terms of Clearance: N/A.

A. Justification

1. Circumstances Making the Collection of Information Necessary

This is a request for OMB approval of the information collection requirements in the Orphan Drug Regulations: Proposed rule.

Abstract: The Food and Drug Administration (FDA) is proposing to amend the 1992 Orphan Drug Regulations, 21 CFR Part 316. The 1992 regulations were issued to implement sections 525 through 528 of the Orphan Drug Act Amendments to the Food, Drug, and Cosmetic Act. The 1992 regulations specify the procedures for sponsors of orphan drugs to use in obtaining the incentives provided for in the Act and set forth the procedures that FDA will use in administering the Act.

The proposed amendments are intended to clarify regulatory provisions and make minor improvements to address issues that have arisen since the issuance of the regulations in 1992. They 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. Except with respect to the two proposed revisions addressed below, the revisions in this proposed rule clarify existing regulatory language and do not constitute a substantive or material modification to the approved collections of information in current part 316 (Cf. 5 CFR 1320.5(g). The collections of information in current part 316 have been approved by OMB in accordance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520), under OMB control number 0910-0167.

One proposed revision is a requirement that sponsors include in orphan-drug designation requests a chemical or meaningful descriptive name of the drug, if neither a trade name nor a generic name is available. As provided in § 316.20(b)(2), requests for orphan-drug designation must currently include the generic and trade name, if any, of the drug. For some products, however, neither a generic, nor trade name may be available. This can be the case for some large and complicated biological products or for any molecule for which the sponsor has not yet obtained a trade name. FDA is proposing to revise § 316.20(b)(2) so that, if neither such name is available, requests for designation include a chemical name or a meaningful descriptive name. Drug names need to be meaningful to the public because the Orphan Drug Act requires that notice respecting designation of a drug be made available to the public (section 526(c) of the FD&C Act and 21 CFR § 316.28). Internal business codes or other similar identifiers do not suffice for publication

purposes as they do not provide meaningful notice to the public of a designation. By providing such information in the request for designation, sponsors would help ensure that the name that FDA ultimately publishes under § 316.28 upon designation of the product is accurate and meaningful.

FDA regulations are currently silent on when sponsors must respond to a deficiency letter from FDA on an orphan-drug designation request. FDA sends such deficiency letters when a request lacks necessary information or contains inaccurate information, for example, a miscalculated prevalence estimate. Another proposed revision to § 316.24(a) is a requirement that sponsors respond to deficiency letters from FDA on designation requests within 1 year of issuance of the deficiency letter, unless within that timeframe the sponsor requests in writing an extension of time to respond. FDA will grant all reasonable requests for an extension. In the event the sponsor fails to respond to the deficiency or request an extension of time to respond within the 1-year timeframe, FDA may consider the designation request voluntarily withdrawn. This proposal is necessary to ensure that designation requests do not become "stale" by the time they are granted, such that the basis for the initial request may no longer hold.

This information collection is not related to the American Recovery and Reinvestment Act of 2009 (ARRA).

2. Purpose and Use of the Information Collection

Orphan-drug designation provides financial incentives for the development of a drug for the diagnosis, prevention, or treatment of a rare disease or condition. A request for orphan drug designation can be made using FDA form 3671, which is the "common form" for orphan drug designation requests for the FDA and European Medicines Agency (EMA). Irrespective of whether FDA form 3671 is used, an orphan drug designation application submitted to FDA must comply with 21 CFR Part 316 (specifically 21 CFR 316.20 content and format of a request for orphan-drug designation).

The proposed revision that sponsors include in orphan-drug designation requests a chemical or meaningful descriptive name of the drug, if neither a trade name nor a generic name is available**,** can be submitted on FDA form 3671.

The proposed amendment that sponsors request an extension of time to respond to an orphan deficiency letter needs to be in writing and does not require FDA form 3671.

FDA uses the requested information to make the determination that the drug is for a legitimately rare disease or condition and issue an orphan-drug designation.

If orphan-drug designation is issued, a chemical name or a meaningful descriptive name, if neither a generic nor trade name were available, will ensure that the notice is meaningful, such that individuals, patients, health care providers, sponsors, and other stakeholders can identify which drug has been designated as an orphan drug. This information can be used by: (1) Individuals or households, (2) Private Sector (business and not-for profit) (3) State, Local or Tribal Governments, (4) Federal Government.

3. Use of Improved Information Technology and Burden Reduction

   Improved technology for filing of pre-clinical and clinical information is currently being considered by operating drug and biological review Centers in FDA. Changes made in such technologies will be adopted when appropriate within the procedures of FDA drug review and orphan products development programs.

4. Efforts to Identify Duplication and Use of Similar Information

   Since the collection of data is specifically for application for incentives under the Orphan Drug Act, there is little possibility that other agencies are collecting similar information.

5. Impact on Small Businesses or Other Small Entities

   This proposed rule primarily clarifies current practice and any costs would be very small. FDA proposes to certify that the final rule will not have a significant economic impact on a substantial number of small entities.

6. Consequences of Collecting the Information Less Frequently

   The frequency of the collection of the data is entirely controlled by the sponsor requesting eligibility for the orphan-drug designation incentive of the Orphan Drug Act. There are no legal obstacles to reduce the burden.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

   There are no special circumstances for this collection of information.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

   As required by section 3506(c)(2)(B) of the Paperwork Reduction Act of 1995 (PRA), FDA provided an opportunity for public comment on the information collection requirements of the proposed rule that published in the FEDERAL REGISTER on October 19, 2011.

   Orphan products staff regularly attends public meetings of industry organizations, clinical investigators, patient groups, and other similar events. No comments or suggestions relative to the requirements have been received through this source. In addition, FDA maintains an active Web Site and a toll-free phone line for its orphan product program where concerns about the requirements or their modification can be readily submitted and has received none.

9. Explanation of Any Payment or Gift to Respondents

   There are no payments or gifts provided to respondents.

10. Assurance of Confidentiality Provided to Respondents

The Orphan Drug Act provides that the designation of a drug as an orphan drug should be a public event. Accordingly, 21 CFR 316.28 provides that public notice be made of all drugs designated as orphan-drugs and will include the name and address of the sponsor, the name of the drug, the rare disease or condition for which the drug was designated, and the proposed indication for use.

11. Justification for Sensitive Questions

No questions of a sensitive nature are contained in the proposal.

12. Estimates of Annualized Burden Hours and Costs

12 a. Annualized Hour Burden Estimate

Table 1 – Estimated Annualized Burden Hours

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average burden per Response	*Total Hours*
316.20(b)(2)	20	1	20	0.2 (12 minutes)	*4*
316.24(a)	10	1	10	2	*20*
Total					*24*

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).

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

12b. Annualized Cost Burden Estimate

Table 2 – Cost to Respondents			
Type of Respondent	Total Burden Hours	Hourly Wage Rate	Total Respondent Costs
Regulatory Affairs Specialist	20	$46.00	$920
Total			$920

FDA proposes to modify and clarify the requirements for the drug name. Current regulations in § 316.20(b)(2) 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. FDA proposes to require that a drug that has neither a generic nor a trade name be identified according to its chemical name or a meaningful descriptive name (i.e., one that would be meaningful to the public if published). Descriptive names are readily accessible to the sponsor and could be included in a designation request as easily as an internal business code and any costs would be too small to meaningfully quantify.

FDA proposes a 1-year time limit for sponsors to respond to deficiency letters or obtain a time extension (§ 316.24(a)). Based on FDA 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. FDA knows of no public health benefit from open inactive designation requests. FDA does not know if they exist because sponsors gain nothing from the cost of formally withdrawing a request or because there may be a strategic advantage to an inactive request for designation. Current regulations do not impose time limits on sponsors replying to FDA deficiency letters and FDA has no mechanism to encourage sponsors to continue to actively pursue designation. Sponsors who would otherwise respond to a deficiency letter within 1 year would be unaffected by this proposal. Sponsors actively pursuing designation but needing more than 1 year to respond to a deficiency letter would be expected to submit a time extension request to FDA. FDA assumes approval for all extension requests from sponsors actively pursuing orphan-drug designation and estimates a request would require 2 hours of time from a regulatory affairs specialist. At a benefit-adjusted hourly wage of $46, the cost to submit an extension request is $92. Based on the FDA experience with deficiency letters and the frequency of responses requiring more than 1 year, FDA estimates 10 requests for additional time each year. The estimated annual cost of this provision is $920. FDA assumes sponsors not actively pursuing designation would not obtain extensions and their requests would be considered to be withdrawn 1 year after the deficiency letter. FDA does 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, FDA estimates 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.

13. Estimates of Other Total Annual Costs to Respondents and/or Recordkeepers/Capital Costs

    There is no capital, start-up, operating or maintenance costs associated with this information collection.

14. Annualized Cost to the Federal Government

    FDA estimates no additional costs to the Federal Government associated with collecting a chemical name or a meaningful descriptive name.

    FDA proposes a 1-year time limit for sponsors to respond to deficiency letters or obtain a time extension (§ 316.24(a)). 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. FDA assumes approval for all extension requests from sponsors actively pursuing orphan-drug designation and estimates a request FDA estimates that each request would require 1 hour of time from a GS-14 Regulatory Management Officer to collect and process the request. At a benefit-adjusted hourly wage of $65, the cost to collect and process each extension request is $65. Based on the experience with deficiency letters and the frequency of responses requiring more than 1 year, FDA estimates 10 requests for additional time each year. The estimated annual cost to the Federal Government will be $650.

    The estimates are based on knowledge of resources used by the FDA Office of Orphan Products Development in implementing the Orphan Drug Act over the last 28 years. Since the number of applications for orphan-drug designation are expected to continue at the same annual rate, past FDA experience will be a good predictor of future resource needs.

15. Explanation for Program Changes or Adjustments

    This is a new data collection.

16. Plans for Tabulation and Publication and Project Time Schedule

    Section 316.28 requires that FDA publish a monthly updated list of designated drugs in addition to placing on file at the FDA Division of Dockets Management an annual cumulative list of all designated drugs. FDA makes available a cumulative list of all designated drugs to date and a cumulative list of designated drugs in the current year on its Web site. These lists are updated monthly. To identify a drug in these lists and in the docket, FDA publishes its generic name and trade name, if any. If neither name is available, FDA currently publishes the chemical name or a meaningful descriptive name of the drug (i.e., a name that would be meaningful to the public). FDA proposes to revise § 316.28 to reflect FDA's existing publication practices.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

    FDA is not seeking approval to exempt display of the expiration date for OMB approval.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.