Orphan Drug Products; Common EMA/FDA Application Form for Orphan Medicinal Product Designation (Form FDA 3671)

Amendment to OMB No. 0910-0167

SUPPORTING STATEMENT

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, 21 CFR Part 316. These provisions implement sections 525 through 528 of the Orphan Drug Act Amendments to the Food, Drug, and Cosmetic Act. These 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.

Section 525 of the Act (21 USC 360aa) requires the Agency to provide written recommendations on studies required for approval of a marketing application for a drug for a rare disease or condition. Section 526 of the Act (21 USC 360bb) provides for designation of drugs as orphan drugs when certain conditions are met. Section 527 of the Act (21 USC 360cc) provides conditions under which a sponsor of an approved orphan drug enjoys exclusive FDA marketing approval for that drug for the orphan indication for a period of seven years.

Section 528 of the Act (21 USC 360dd) is to encourage sponsors to make investigational orphan drugs available for treatment of persons in need on an open protocol basis before the drug has been approved for general marketing. Open protocols may permit patients who are not part of the formal clinical investigation to obtain treatment where adequate supplies exist and no alternative effective therapy is available.

These regulations describe the information to be submitted by sponsors to request eligibility for the incentives by implementing a program as outlined in the Orphan Drug Act. The following provisions identify the information collections contained in the regulation.

21 CFR 316.10 – Content and format of a request for written recommendations (Reporting)
Specifies the procedures a sponsor is to follow when requesting a written recommendation from FDA concerning the clinical and non-clinical investigations necessary for the approval of a marketing application.

21 CFR 316.12 – Providing written recommendations (Reporting)
Specifies that prior to receiving a written recommendation from FDA, a sponsor may

be required to submit for Agency review, the results of non-clinical studies or completed early clinical studies.

21- CFR 316.14- Refusal to provide written recommendations (Reporting)
Specifies detailed procedures to be followed by a sponsor when FDA refuses to provide a written recommendation.

21 CFR 316.20 – Content and format of a request for orphan-drug designation (Reporting)
Specifies the content and format a sponsor must submit in a request for orphan-drug designation. The Common European Medicines Agency (EMEA)/Food and Drug Administration (FDA) Application Form for Orphan Medicinal Product Designation (Form FDA 3671) is intended to benefit sponsors who desire to seek orphan designation of drugs intended for rare diseases or conditions from both the European Commission and FDA by reducing the burden of preparing separate applications to meet the regulatory requirements in each jurisdiction. Any sponsor seeking orphan designation of the same drug for the same disease or condition from both FDA and EMEA may use this common application form for regulatory filing purposes. A sponsor may also use this common application form when seeking designation only from FDA. This common application form is intended to complement, not supersede, the relevant regulatory frameworks currently in effect. When using this common application form, the sponsor must comply with all applicable regulatory requirements in each jurisdiction in which designation is sought. To use the common application form, the sponsor must provide the required information in each applicable section as instructed in the explanatory notes. Certain information elements are identified in the form as required exclusively by either FDA or EMEA regulations, and as such, they must be included only in the application to that jurisdiction.

21 CFR 316.21 – Verification of orphan-drug status (Reporting)
Specifies the content and format a sponsor must follow when seeking to obtain orphan drug designation of a drug for a disease or condition affecting less than 200,000 persons in the United States.

21 CFR 316.22 – Permanent-resident agent for foreign sponsor (Reporting)
Requires that a foreign sponsor seeking orphan drug designation nominate a permanent resident-agent and the name of the resident agent shall be submitted to the FDA's Office of Orphan Products.

21 CFR 316.26 – Amendment to orphan-drug designation (Reporting)
Specifies the requirements to use when a sponsor wishes to apply for an amendment to an orphan drug designation prior to approval of the marketing application.

21 CFR 316.27 – Change in ownership of orphan-drug designation (Reporting)
Specifies information to be submitted to FDA during a change of ownership of the orphan drug designation.

21 CFR 316.30 – Annual reports of holder of orphan-drug designation (Reporting)
Requires that within 14 months after a drug is designated as an orphan drug (and annually, thereafter), the sponsor shall submit a brief progress report to FDA until marketing approval.

21 CFR 316.36 – Insufficient quantities of orphan drugs (Reporting)
Specifies that a sponsor seeking to retain orphan-drug exclusivity, after an FDA determination, cannot assure the availability of sufficient quantities of an orphan-drug to meet the needs of affected persons.

21 CFR 316.24 - Deficiency letters and granting orphan-drug designation (Reporting)
(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.

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.

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. Secondly, the information describes the sponsor's plan for clinical and preclinical studies.

Review of the sponsor's protocol will allow the Agency to provide guidance to the sponsor that may allow him to eliminate plans for costly and unnecessary studies. FDA may also suggest adding studies or making other changes that will result in a plan that conforms to FDA requirements. Data obtained from well-designed studies will be, therefore, useful in demonstrating safety and effectiveness of the drug for the rare disease or condition. Failure to collect this information will seriously impair the FDA's ability to guide the sponsor needing such recommendations, and may result in the sponsor dedicating substantial resources and losing valuable time in doing studies that are not necessary or are irrelevant to obtaining FDA market approval.

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

The provisions of the Orphan Drug Act and the provisions contained in the regulations are favorable to small business interests. The orphan-drug designation provision entitles the sponsor to Federal income tax credits for clinical studies, and eligibility for grants to fund studies of orphan products. The Orphan Drug Exclusivity Provision provides protection from competition by other companies that is administered by FDA. The FDA must by law insure that a competitive product does not enter the market by withholding approval of a subsequent new drug application or biological license.

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 one of the incentives 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

The method of collection is consistent with the guidelines of 5 CFR 1320.6. 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

In accordance with 5 CFR 1320.8(d), FDA published a 60-day notice for public comment on the information collection provisions was published in the Federal Register of April 16, 2014 (79 FR 21471) to which no comments were received.

The Orphan Products Development 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 website and toll-free phone line for its orphan product program where concerns about the requirements or their modifications 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. Similarly, public notice is made identifying sponsors' drugs and indications for use that have obtained Orphan Drug Exclusivity. 21 CFR 316.32 provides that FDA will neither publicly disclose the existence of a request for nor the substance of the request until final action is taken. Further, FDA will not publicly disclose the existence of a pending marketing application for a designated orphan drug unless the existence of the request has been previously disclosed or acknowledged.

Determinations of public availability of data and information contained in pending and approved marketing applications will continue to be in accordance with existing provisions of 21 CFR Parts 20 and 314.430.

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 and Cost

Table 1. – Estimated Annual Reporting Burden[1]

21 CFR Section & FDA Form No.	Annual No. of Respondents	No. of Responses Per Respondent	Total Annual Responses	Average Burden per Response (in hours)	Total Hours
Written recommendations; content and format of a request, the providing of; refusal to provide 316.10, 316.12, & 316.14	2	1	2	100	200

Content and format of a request for designation; verification of status; amendment to designation 316.20, 316.21, 316.26 & Common European Medicines Agency/Food and Drug Administration Application Form Form FDA 3671	225 50	2 3	450 150	150 45	67,500 6,750
Permanent resident agent for foreign sponsor 316.22	65	1	65	2	130
Changes in ownership of orphan drug designation 316.27	43	1	43	5	215
Annual reports of holder of orphan drug designation 316.30	450	1	450	3	1,350
Insufficient quantities of orphan drugs 316.36	1	3	6	15	90
Deficiency letters and granting orphan-drug designation 316.24(a)	10	1	10	2	20

Total	76,255

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

The information requested from respondents represents, for the most part, an accounting of information already in the possession of the applicant. It is estimated, based on frequency of requests over the past three years, that 275 persons or organizations per year will request orphan drug designation and five will request formal recommendations on design or preclinical or clinical studies.

FDA estimates that the effort required to prepare the applications for consideration in both sections 525 and 526 (21 CFR Parts 316.10 & 316.20, respectively, and Form FDA 3671) is generally similar, and, is estimated to require an average of 105 hours of professional staff time and 45 hours of support staff time per application (105 + 45 =150). Estimates of annual activity and burden for foreign sponsor nominations of a resident agent, change in ownership of designations, and inadequate supplies of a drug in exclusivity, are based on total experience by FDA with such requests since 1983.

For 316.10, 316.12, and 316.14, two requests for recommendations are anticipated.

For 316.20, 316.21, and 316.26 - **450** responses related to Designation as Orphan Drug Annually x 150 hours per response (105 hours professional time + 45 hours support time) = 67,500 hours.

For FDA Form 3671- **150** respondents annually x 45 hours per response (25 hours professional time + 20 hours support time) = 6,750 hours.

For 316.22 - **65** nominations annually x 2 hours per response (1 hour professional time + 1 hours support time) = 130 hours.

For 316.27 - **43** changes annually x 5 hours per response (2 hours professional time + 3 hours support time) = 215 hours.

For 316.30 - **450** reports annually x 3 hours per response (1 hour professional time + 2 hours support time) = 1,350 hours.

For 316.36 - **6** responses annually x 15 hours per response (10 hours professional time + 5 hours support time) = 90 hours.

For 316.24 – **10** responses annually x 2 hours per response = 20 hours.

12b. Annualized Cost Burden Estimate

Activity	No. of Hours	Cost per Hour	Total Cost

Request for orphan Designation	67,500	Professional $85 Support Staff 25	5,737,500 1,687,500
Common Request/ Form FDA 3671	6,750	Professional $85 Support Staff 25	573,750 168,750
Foreign Sponsor Nominate	130	Professional $85 Support Staff 25	11,050 3,250
Change in Ownership	215	Professional $85 Support Staff 25	18,275 5,375
Annual Report	1,350	Professional $85 Support Staff 25	114,750 33,750
Inadequate Supplies	90	Professional $85 Support Staff 25	7,650 2,250
TOTAL			8,363,850

For purposes of calculating costs to respondents, we utilized an estimated average for professional response time at $85.00 per hour and $25.00 per hour for support hour. These estimates are based on the Department of Labor's salary tables for scientific professionals and administrative personnel. The hourly input per requirement utilizes the information in the preceding table.

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

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

14. Annualized Cost to the Federal Government

FDA estimates that the equivalent of five full time positions ranging from GS-5 clerical personnel to GS-15 medical officers ($178,875 for personnel cost and benefits and $10,000 or operating funds per year at a total cost of $566,625) will be required to fully implement the collection of information, response to applicants, guidance and recommendation to sponsors required by the applicable law and regulations. 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 30 years. Since the number of applicants is expected to continue to increase rapidly, past FDA experience will be a good predictor of future resources.

15. Explanation for Program Changes or Adjustments

This ICR contains both a program change and adjustment to the burden.

The program change represents the consolidation of 0910-0702, a final rule that was submitted to and approved by OMB in 2013. This final rule incorporated two changes in the regulations and the addition of form FDA 3671:

1. Under § 316.20(b)(2) as revised, requests for designation must include a chemical name or a meaningful descriptive name of the drug if neither a generic nor trade name is available.

2. The final rule revised § 316.24(a) (Granting orphan-drug designation) to include 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.

These revisions (program changes) are included in:

IC#2 – 316.20 (content and format of a request for designation; verification of status; amendment to designation), increase of 22 responses and 3300 burden hours

IC#7 – new form FDA 3671 (Common European Medicines Agency/Food and Drug Administration Application Form), increase of 150 increases and 45 burden hours

IC#8 – 316.24 (deficiency letters and granting orphan-drug designation), an increase of 10 responses and 20 burden hours

The total, therefore, due to program change is 6,529.

The adjustment in burden is based on data FDA has received over the last three years.

16. Plans for Tabulation and Publication and Project Time Schedule

The objectives of the collection are not for publication of statistical material and do not employ statistical methods.

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

Not applicable.