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

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 – Changes 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.

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. The respondents to this collection of information are biotechnology firms, drug companies, and academic clinical researchers. 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.

8a. Comments in Response to the Federal Register Notice

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 January 21, 2011, (76 FR 3910) to which no comments were received.

8b. Efforts to Consult Outside the Agency

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.

12a. Annualized Hour Burden Estimate

Table 1. – Estimated Annual Reporting Burden

21 CFR Section and FDA Form	No. of Respondents	No. of Responses per Respondent	Total Annual Responde nts	Average Burden per Response (in hours)	Total Hours
316.10, 316.12, & 316.14	2	1	2	100	200
316.20, 316.21, & 316.26 Form FDA 3671	214	2	428	150	64,200
316.22	55	1	55	2	110
316.27	43	1	43	5	215

316.30	1,652	1	1,652	3	4,956
316.36	1	3	3	15	45
Total					69,726

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 five years, that 214 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 108 hours of professional staff time and 42 hours of support staff time per application (108 + 42 +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, 428 responses related to Designation as Orphan Drug Annually x 150 hours per response (108 hours professional time + 42 hours support time) = 64,200 hours.

For 316.22, 55 nominations annually x 2 hours per response (1 hour professional time + 1 hours support time) = 110 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, 1,652 reports annually x 3 hours per response (1 hour professional time + 2 hours support time) = 4,956 hours.

For 316.36, 3 responses annually x 15 hours per response (10 hours professional time + 5 hours support time) = 45 hours.

12b. Annualized Cost Burden Estimate

Activity	Number of Hours	Cost per Hour	Total Cost

Request for Designation	200	Professional $85 Support staff $20	17,000 4,000
Common Request for Designation from EMEA and FDA Form 3671	64,200	Professional $85 Support Staff $20	5,457,000 1,284,000
Foreign Sponsor Nominate	110	Professional $85 Support Staff $20	9,350 2,200
Change in Ownership	215	Professional $85 Support Staff 20	18,275 4,300
Annual Report	4,956	Professional $85 Support Staff $20	421,260 99,120
Inadequate Supplies	45	Professional $85 Support Staff $20	3,825 900
Total			$7,321,230

For purposes of calculating costs to respondents, we utilized an estimated average for professional response time at $85.00 per hour and per hour costs for support hour at $20.00. These estimates are based on discussions with prior respondents related to the salary levels and types of personnel assigned to obtain and present the information required. 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 costs and benefits and $10,000 of 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 recommendations 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 27 years. Since the number of applications is expected to continue to increase rapidly, past FDA experience will be a good predictor of future resource needs.

15. Explanation for Program Changes or Adjustments

The adjustment in burden is due to the increase in the number of respondents. The adoption by FDA and the European Medicines Agency (EMEA) of the Common EMEA/FDA Application Form for Orphan Medicinal Product Designation (form FDA 3671) has caused the number of respondents to increase. This common application form has reduced the preparation burden of separate applications for sponsors who desire to seek orphan designation of drugs intended for rare diseases or conditions from both the European Commission and FDA and still meet the regulatory requirements in each jurisdiction.

16. Plans for Tabulation and Publication and Project Time Schedule

Not applicable.

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.