UNITED STATES FOOD & DRUG ADMINISTRATION

Orphan Drugs; 21 CFR 316

OMB Control No. 0910-0167 – Extension

SUPPORTING STATEMENT **Part A – Justification**:

1. Circumstances Making the Collection of Information Necessary

This information collection helps support implementation of sections 525, 526, 527, and 528 of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 360aa, 360bb, 360cc, and 360dd), as well as related guidance and agency forms. Sections 525, 526, 527, and 528 of the FD&C Act pertain to the development of drugs for rare diseases or conditions, including biological products and antibiotics, otherwise known or referred to as "*Orphan Drugs*." Specifically, section 525 of the FD&C Act requires written recommendations on studies required for approval of a marketing application for a drug for a rare disease or condition. Section 526 of the FD&C Act provides for designation of drugs as orphan drugs when certain conditions are met; section 527 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 7 years; and, finally, section 528 is intended 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.

Agency regulations in part 316 (21 CFR part 316) subpart A identify the scope of coverage, applicable definitions, and statutory provisions applicable to orphan drugs. The regulations in 21 CFR part 316, subpart B (316.10 through 316.14) set forth content and format elements for written recommendation requests, and discuss FDA providing or refusing to provide the requested written recommendations. Similarly, regulations in 21 CFR 316 subpart C (316.20 through 316.30) prescribe content and format elements for requesting orphan drug designation; identify submission schedules for requisite information including amendments, updates, and reports; and provide for publication and revocation of orphan drug designation. Regulations in 316 subparts D and E (316.31-316.40) address orphan drug exclusive approval and open protocols for investigations, respectively. Finally, regulations in 316 subpart F (316.50 through 316.52) provide for the issuance of guidance documents that apply to the Orphan Drug provisions of the FD&C Act and regulations in part 316. The list is maintained on the internet and guidance documents are issued in accordance with our Good Guidance Practice regulations in 21 CFR 10.115, which provide for public comment at any time.

The information collection includes **Form FDA 3671**, Common EMEA/FDA Application for Orphan Medicinal Product, and **Form FDA 4035**, FDA Orphan Drug Designation Request Form, intended to benefit sponsors who desire to seek orphan designation of drugs intended for rare diseases or conditions from FDA. The form is a simplified method for sponsors to provide only the information required by § 316.20 for FDA decision making. Orphan drug designation

requests and related submissions (amendments, annual reports, etc.), humanitarian use device designation, and rare pediatric disease designation requests and submissions may be submitted electronically by email to the OOPD.

We also include the document entitled, "*Meetings with the Office of Orphan Products Development: Guidance for Industry, Researchers, Patient Groups, and Food and Drug Administration Staff,*" (July 2015), available for download at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/meetings-office-orphan-products-development. It provides recommendations to industry, researchers, patient groups, and other stakeholders interested in requesting a meeting, including a teleconference, with our Office of Orphan Products Development (OOPD) on issues related to orphan drug designation requests, humanitarian use device designation requests, rare pediatric disease designation requests, funding opportunities through the Orphan Products Grants Program and the Pediatric Device Consortia Grants Program, and orphan product patient related topics of concern. It is also intended to assist OOPD staff in addressing such meeting requests. The guidance describes procedures for requesting, preparing, scheduling, conducting, and documenting such meetings and discusses background information we recommend be included in such requests.

We are therefore requesting extension of OMB approval for information collection found in 21 CFR 316, the applicable forms, and the associated guidance document, as discussed in this supporting statement.

2. Purpose and Use of the Information Collection

Description of Respondents: Respondents to the information collection are sponsors who develop investigational drugs and biologicals for commercial use and who seek orphan drug designation, and upon approval or licensure, orphan drug exclusivity.

As we communicate on our website, over 7,000 rare diseases affect more than 30 million people in the United States. Many rare conditions are life-threatening and most do not have treatments. Drug, biologic, and device development in rare diseases is challenging for many reasons, including the complex biology and the lack of understanding of the natural history of many rare diseases. The inherently small population of patients with a rare disease can also make conducting clinical trials difficult. Since the Orphan Drug Act was signed into law in 1983, the FDA has approved hundreds of drugs for rare diseases, but most rare diseases do not have FDA-approved treatments. The FDA works with many people and groups, such as patients, caregivers, and drug and device manufactures, to support rare disease product development.

3. Use of Improved Information Technology and Burden Reduction

As we communicate on our website at https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products, respondents may submit orphan drug designation requests electronically through the CDER NextGen portal or by emailing the required information to orphan@fda.hhs.gov; or by mailing

the required information to the OOPD at the address found on our website. New users of the CDER NextGen Portal must register for an account. For designation requests submitted by email, the agency recommends using automated read receipt to verify receipt of the email. Sponsors and others who plan to email information to FDA that is private, sensitive, proprietary or commercial confidential are strongly encouraged to send it from an FDA-secured email address so the transmission is encrypted. The agency will assume the addresses of emails received or email addresses provided as a point of contact are secure when responding to those email addresses. Sponsors and others can establish a secure email address link to FDA by sending a request to SecureEmail@fda.hhs.gov. There may be a fee to a commercial enterprise for establishing a digital certificate before encrypted emails can be sent to FDA.

4. Efforts to Identify Duplication and Use of Similar Information

We are unaware of duplicative information collection.

5. Impact on Small Businesses or Other Small Entities

The information collection poses no undue burden on small entities. Also, provisions of both the Orphan Drug Act and those found in the applicable regulations are favorable to small business interests. The orphan-drug designation provision entitles the sponsor to: (1) Federal income tax credits for qualified clinical trial expenses; (2) waiver of application fees; and (3) eligibility for grants to fund studies of orphan products. The Orphan Drug Exclusivity Provision provides protection from competition by other companies for the same drug for the same indication or use. The FDA must by law ensure that a competitive product does not enter the market by withholding approval of a subsequent new drug application or biological license. Finally, OOPD staff is available to respondents to assist with the information collection.

6. Consequences of Collecting the Information Less Frequently

The information collection schedule is consistent with statutory and regulatory requirements, as well as recommendations found in agency guidance. The frequency is driven by respondents who seek an Orphan Drug product designation.

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

The method of collection is consistent with the guidelines of 5 CFR 1320.5. 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

In accordance with 5 CFR 1320.8(d)(1), we published a 60-day notice soliciting public comment on the information collection in the *Federal Register* of June 13, 2023 (88 FR 38513). Although we received one comment, it was not responsive to the information collection topics solicited and was therefore not addressed in our 30-day notice of December 4,

2023 (88 FR 84148).

9. Explanation of Any Payment or Gift to Respondents

There are no payments or gifts provided to respondents however, as noted in Question 5, tax incentives exist intending to promote the development of Orphan Drug products.

10. Assurance of Confidentiality Provided to Respondents

Consistent with 5 CFR 1320.5(d)(2)(vii) and agency regulations in 21 CFR § 20.20, data will be kept private to the extent allowed by law:

The Privacy Act of 1974

In preparing this supporting statement, we consulted our Privacy Office to ensure appropriate identification and handling of information collected. Although this ICR collects personally identifiable information (PII) or other data of a personal nature, it is collected in the context of the subject individuals' professional capacity and the FDA-related work performed for their employer (e.g., point of contact at a regulated entity). The PII submitted via **Form FDA 4035** (*The Food and Drug Administration Orphan Drug Designation Request Form*) and **Form FDA 3671** (*The Common European Medicines Agency (EMA)/Food and Drug Administration (FDA) Application Form for Orphan Medicinal Product Designation*) is name, business email address, business telephone number, and business fax telephone number. Sponsors seeking orphan designation of the same drug for the same disease or condition from both FDA and EMA may use this common application form for regulatory filing purposes. The Food and Drug Administration Orphan Drug Designation Request Form 4035 is intended to benefit sponsors who desire to seek orphan designation of drugs intended for rare diseases or conditions from only FDA. Both forms are intended to complement, not supersede, the relevant regulatory frameworks currently in effect. When using the common application form, the sponsor must comply with all applicable regulatory requirements in each jurisdiction in which designation is sought.

The Freedom of Information Act (5 U.S.C. 552)

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. Finally, 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

12a. Annualized Burden Hours:

Table 1: Estimated Annual Recordkeeping Burden[1]

21 CFR section; activity	No. of Respondents	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Record	Total Hours
21 CFR § 316 associated records	780	1.25	975	135	131,625
§§ 316.20, 316.21, 316.26 (Form FDA 4035)	780	1.25	975	32	31,200
§ 316.22; Notifications of changes in agents	300	1	300	0.5	150
§ 316.24(a); Deficiency letters and granting orphan-drug designation	363	1	20	2	40
§ 316.27; Submissions to change ownership of orphan drug designation	90	1	90	3	270
§ 316.30; Annual reports	2,039	1	2,039	3	6,117
§ 316.36; Assurance of the availability of sufficient quantities of the orphan drug; holder's consent for the approval of other marketing applications for the same drug	1	3	3	15	45
Guidance Recommendations: Meeting requests to OOPD and related submission packages	807	1.5	1,211	4	4,842
TOTAL			0		0

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

Our burden estimate includes those activities related to: (1) requesting orphan drug designation; (2) responding to deficiencies letters with submissions of amendments; (3) keeping files current with contact information for agents and transfer of ownership, when applicable; (4) submitting annual reports while products have designation status; and (5) requesting and preparing for both informal and formal meetings. Because the PRA defines a recordkeeping requirement to include reporting those records to the Federal government, we account for these activities cumulatively in Table 1 above.

12b. Annualized Cost Burden Estimate

To calculate burden costs, we assume wages commensurate to those for a regulatory professional in the Washington DC area and factor this by the total number of annual burden hours. Using data from the Bureau of Labor Statistics, we therefore calculate a loaded hourly wage rage of $85.00 and factor that by 272,850 hours for a total of $21,189,700 annually.

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

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

14. Annualized Cost to the Federal Government

Resource allocations are based on factoring wage rates for positions ranging from GS-12 clerical personnel to GS-15 medical officers ($1,520,000 for personnel costs and benefits and $3,000 for operating costs per year). We currently estimate costs at $2,750,000 based on submissions to the agency.

15. Explanation for Program Changes or Adjustments

We have adjusted our burden estimate to reflect an overall **increase of 50,616 hours** and **1,036 records** annually, noting an inadvertent error in our *Federal Register* notice which communicated an increase of only 766 hours, although the summary burden table was presented correctly. We attribute the adjustment to an increase in the number of submissions, amendments, and annual reports, as well as a comprehensive evaluation of the information collection.

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

Display of the OMB Expiration Date is appropriate. Consistent with established practice, FDA publishes a Federal Register notice announcing OMB approval of information collection associated with the guidance document specifically discussed in this supporting statement and displays in that notice both the OMB control number and its current expiration date. In addition, FDA displays the OMB control number on the guidance document cover page and includes a link to www.reginfo.gov to identify the current expiration date.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.