UNITED STATES FOOD AND DRUG ADMINISTRATION

Drug Establishment Registration and Drug Listing Requirements for Establishments Engaged in Distributed Manufacturing and Certain Foreign Establishments

RIN 0910-AI94

OMB Control Number 0910-NEW

SUPPORTING STATEMENT

Part A: Justification:

1. Circumstances Making the Collection of Information Necessary

This request is being submitted in support of agency rulemaking in accordance with 5 CFR 1320.11. Agency regulations implementing drug establishment and registration provisions are found in part 207 (21 CFR part 207) and include reporting and recordkeeping requirements. The proposed rulemaking entitled, "Drug Establishment Registration and Drug Listing Requirements for Establishments Engaged in Distributed Manufacturing and Certain Foreign Establishments" (the proposed rule), if finalized, would revise the current registration regulations in part 207 to distributed manufacturing establishment provide clear instructions specific to registering a distributed manufacturing establishment (DME). The information required to register a DME would include the same categories of registration requirements that are applicable to establishments engaged in traditional manufacturing, with appropriate revisions to account for differences between DMEs and establishments engaged in traditional manufacturing. The proposed rule would eliminate duplicate submission of registration information by not treating distributed manufacturing units (DMUs) within a DME as individual establishments requiring separate registrations. The proposed rule would also explicitly provide that registrants of a DME inform FDA of the relocation of a DMU in advance of the move as opposed to the current requirement to notify FDA up to 30 days after a change in address.

The proposed rule, if finalized, would also align drug establishment registration and drug listing regulations applicable to foreign drug establishments with clarifying changes to statute made by section 2511 of the Prepare for and Respond to Existing Viruses, Emerging New Threats, and Pandemics Act (PREVENT Pandemics Act). Namely, the proposed rule would clarify the requirement of registration of foreign establishments that manufacture, prepare, propagate, compound, or process a drug that is imported or offered for import into the United States, regardless of whether the drug first undergoes further manufacture, preparation, propagation, compounding, or processing at a separate establishment outside the United States. The proposed rule would also clarify that such foreign establishments must list such drugs. The changes made by the PREVENT Pandemics Act to section 510 of the Food, Drug, and Cosmetic Act (FD&C Act) only clarified existing requirements, and we note that these statutory provisions are self-implementing even in the absence of the proposed rule.

This proposed rule is necessary to provide clear instructions specific to registering DMEs to eliminate duplicate submission of registration information. This proposed rule is also necessary to update the drug establishment registration and listing regulations for foreign establishments to

align them with the recent clarifying changes to the statute made by section 2511 of the PREVENT Pandemics Act.

2. Purpose and Use of the Information Collection

The proposed rule is intended to decrease the regulatory burden for industry, while enabling FDA to obtain the necessary information about manufacturing establishments, in a timely manner, to support FDA programs and public health initiatives. We use drug establishment registration and drug listing information from domestic and foreign establishments to enhance our visibility into the drug supply chain. We also use drug establishment registration and drug listing information from foreign establishments to enhance our ability to prevent the importation of drugs that do not comply with current good manufacturing practice requirements or are otherwise adulterated or misbranded. These statutory provisions provide better visibility into foreign sources of drugs and ingredients, which might enable more narrowly targeted responses to safety concerns related to certain known suppliers. We are also undertaking this rulemaking to establish a registration pathway appropriate for DMEs. As noted, the proposed rule would eliminate duplicate submission of registration information by not treating DMUs within a DME as individual establishments requiring separate registrations.

The information collection is used in support of FDA's mission to protect the public health through postmarketing surveillance for serious adverse drug reactions, inspection of drug manufacturing and processing facilities, monitoring of drug products imported into the United States, and collection of manufacturing amount information. Without the information provided by respondents regarding their drug establishments, we would not be able to adequately protect the public health by assuring their safety and efficacy.

3. Use of Improved Information Technology and Burden Reduction

Electronic reporting is mandatory for this information collection; however, respondents may request waivers in individual cases. Registration of establishments takes place annually during the period beginning on October 1 and ending on December 31. We estimate that all respondents will submit the information electronically, unless exempted.

4. Efforts to Identify Duplication and Use of Similar Information

We are not aware of duplicative information collection.

5. Impact on Small Businesses or Other Small Entities

We do not believe the proposed information collection poses undue burden on small entities. At the same time, FDA has established various agency components to assist small businesses in complying with our regulations. Contact information may be found on our website at https://www.fda.gov/industry/small-business-assistance.

6. Consequences of Collecting the Information Less Frequently

The proposed information collection schedule is consistent with statutory and regulatory requirements.

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

No special circumstances are associated with the information collection.

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

In accordance with 5 CFR 1320.11(a), a statement that the collections of information contained in the proposed rule, and identified as such, have been submitted to OMB for review under 44 U.S.C. 3507(d) of the Act, is included in the preamble to the proposed rulemaking, providing for a 30-day public comment period on the proposed information collection, pursuant to the requirements in 5 CFR 1320.5(a)(1)(iv) and 5 CFR 1320.8(d)(1) and (3). In addition, regarding DME registration, FDA requested and received public comment on FDA's Discussion Paper: Distributed Manufacturing and Point-of-Care Manufacturing of Drugs; Request for Information and Comments (87 FR 62416), which was described in FDA's report, Distributed Manufacturing of Drugs: Stakeholder Feedback and Action Plan (November 2023). The discussion paper and public comments addressed challenges using existing regulatory processes (e.g., establishment registration) that could be a significant burden on both the industry and FDA. The proposed rule incorporates recommendations from industry stakeholders to reduce the burden for manufacturers and provide resource savings for both industry and FDA.

9. Explanation of Any Payment or Gift to Respondents

There are no incentives, payments or gifts associated with this information collection.

10. Assurance of Confidentiality Provided to Respondents

The Privacy Act of 1974 (5 U.S.C. 552a)

In preparing this Supporting Statement, we consulted our Privacy Office to ensure appropriate identification and handling of information collected.

This ICR collects personally identifiable information (PII). PII is collected in the context of the subject individuals' professional capacity and the FDA-related work they perform for their employer (e.g., point of contact at a regulated entity). The PII submitted via the Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution and Manufacturing Amount Information under Section 3112(e) of the Coronavirus Aid, Relief, and Economic Security (CARES) Act is name, work address, and work telephone numbers for the primary contact at a business. FDA determined that although PII is collected, the collection is not subject to the Privacy Act of 1974 and the particular notice and other requirements of the Privacy Act do not apply. Specifically, the FDA does not use name or any other personal identifier to retrieve records from the information collected. Through appropriate webpage design, FDA limited submission fields and minimized the PII collected to protect the privacy of the individuals.

Freedom of Information Act (FOIA)

Under the Freedom of Information Act (FOIA) (5 U.S.C. 552), the public has broad access to government documents. However, FOIA provides certain exemptions from mandatory public disclosure of government records (5 U.S.C. 552(b)(1-9)). FDA will make the fullest possible disclosure of records to the public, consistent with the rights of individuals to privacy, the property rights of persons in trade and confidential commercial or financial information.

11. Justification for Sensitive Questions

The collection of information does not involve sensitive questions.

12. Estimates of Annualized Burden Hours and Cost

Description of Respondents: Respondents to the proposed collection of information are entities who manufacture a drug, or an animal feed bearing or containing a new animal drug, and those who manufacture a drug, or an animal feed bearing or containing a new animal drug that is imported or offered for import into the United States.

12a. Annualized Hour Burden Estimate

We estimate the burden of the collection of information as follows:

Table 1.--Estimated Annual Reporting Burden[1]

Proposed 21 CFR Section; Activity	No. of Eligible Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Distributed Manufacturing					
Proposed § 207.25(b); Registration of DME	10,480	<1	1	1	1
Proposed § 207.29(b); Updates to registration, for DMUs	10,480	<1	4	0.5 (30 minutes)	2
Foreign Drug Establishment Registration and Listing					
21 CFR §§ 207.17, 207.21, and 207.25; Initial foreign establishment registration associated with section 2511 of the PREVENT Pandemics Act	1,313	1.2376	1,625	1.8	2,925
21 CFR § 207.29; Annual review and update of registration information (including expedited updates);	1,313	1.2376	1,625	0.9 (54 minutes)	1,463
21 CFR §§ 207.33, 207.41, 207.45, 207.49, 207.53, 207.54, and 207.55; Initial listing (including National Drug Code (NDC)) associated with section 2511 of the PREVENT Pandemics Act	24,550	1	24,550	2.7	66,285

21 CFR §§ 207.35 and 207.57; June and December review and update (or certification) of listing	24,550	1	24,550	1.35	33,143	[1]
Total			52,355		103,819	

Some figures have been rounded.

Distributed Manufacturing

We base our estimates on our experience with drug establishment registration and updates, the Preliminary Regulatory Impact Analysis (PRIA) (Ref. 9 to the proposed rule), and the hour burden estimates applicable to the existing requirements of part 207, currently approved in OMB control number 0910-0045. If the proposed rule is finalized, DME registrants would be required under proposed § 207.25(b) to submit data elements that differ slightly from those currently required under part 207. Proposed § 207.25(b) would be similar in scope to the information currently required for registration of establishments that are not DMEs but with some notable differences that account for the hub-and-spoke model of a DME, as described in section V.A.4 of the proposed rule. Consistent with our current hour burden estimate for registration approved in OMB control number 0910-0045 (1.0 hour), we estimate that registering a DME will take one hour.

Proposed § 207.29(b) describes the expedited updates for DMEs and the timelines to submit the updates. The same types of expedited updates currently required under § 207.29(a) for establishments that are not DME would apply to DMEs, as well as new categories of expedited updates necessary for DMEs, in particular DMEs with DMUs that can move or be moved. Submissions that would be required on an expedited basis as part of DME registration are nearly identical to those required in current § 207.29(a)(1) for establishments that are not DMEs and follow the same timeline to submit the update no later than 30 calendar days after the change, as discussed in section V.A.5 of the proposed rule. The proposed rule would also explicitly provide that registrants of a DME inform FDA of the relocation of a DMU in advance of the move as opposed to the current requirement to notify FDA up to 30 days after a change in address. Consistent with our current hour burden estimate for updates to registration approved in OMB control number 0910-0045 (0.5 hour), we estimate that updates to registration, for DMUs, will take 0.5 hour.

Our estimate of the number of respondents is based on internal data reflecting 10,480 registered establishments subject to the requirements of part 207. The proposed rule, if finalized, would introduce requirements applicable only to a subset of these 10,480 respondents, specifically those establishments that choose to register as a DME. As discussed in the PRIA, at section II.F.1, we are uncertain as to the likely prevalence of distributed manufacturing in the coming years. We assume that, on average, the drug industry will register zero to two new DMEs in each of the first three years after publication of any final rule. We are also uncertain as to the likely scale of distributed manufacturing operations in the coming years. We assume that, on average, each DME includes four DMUs. As such, the proposed rule would avoid four registrations per DME (as only the fixed distributed manufacturing hub would need to register, in place of four individual units plus the hub). The proposed rule would thereby also avoid a corresponding number of registration renewals per DME in each year after the first. PRIA, at section II.F.1. Based on these assumptions, in the three years following the effective date of a final rule, we estimate that respondents will register one or fewer DMEs and will submit updates for four DMUs, as shown in Table 1. Thereafter, due to the expected cost savings from consolidation of DME registrations and renewals, we project that interest will grow and the drug industry will register three to five new

DMEs in each of the next three years (Years 4-6), and then eight to ten new DMEs per following year (Years 7-10). PRIA, at section II.F.1. We estimate that it will take a respondent one hour to register a DME and 30 minutes to update a registration to include a DMU, as shown in Table 1.

As noted, the proposed rule would also explicitly provide that registrants of a DME inform FDA of the relocation of a DMU in advance of the move as opposed to the current requirement to notify FDA up to 30 days after a change in address. We estimate that the timing of this notification imposes no burden in addition to the usual burden for an update, which would be accounted for as an update to registration for DMUs.

Foreign Drug Establishment Registration and Listing

We base our hour burden estimates on the burden estimates applicable to the existing registration and listing requirements of part 207, currently approved in OMB control number 0910-0045. To account for differences in English proficiency, we multiply the hours estimated for compliance tasks by a factor of 1.8, consistent with the PRIA, section II.K.1. Hence, we estimate about 1.8 foreign labor hours for each hour spent by a US-based worker on tasks involving English proficiency. Section 2511 of the PREVENT Pandemics Act amended section 510 of the FD&C Act to expressly require the registration of foreign establishments that manufacture, prepare, propagate, compound, or process a drug that is imported or offered for import into the United States, regardless of whether the drug undergoes further manufacture, preparation, propagation, compounding, or processing at a separate establishment outside the United States prior to being imported or offered for import into the United States. Section 2511 of the PREVENT Pandemics Act also amended section 510 of the FD&C Act to clarify the requirement that such establishments list such drugs. These self-implementing changes to statute introduced no new requirements on foreign establishments but rather clarified requirements already in effect at the time.

With respect to foreign establishment registration and drug listing requirements in proposed §§ 207.17 and 207.41, if the proposed rule is finalized, we expect that unregistered foreign firms required to register and list with FDA by section 510 of the FD&C Act, as amended by section 2511 of the PREVENT Pandemics Act, would more clearly understand that they are required to register and list. Though changes to statute made by section 2511 of the PREVENT Pandemics Act introduced no new requirements on foreign establishments and only clarified existing requirements, we expect this clarification to increase compliance among covered foreign establishments. As noted, these statutory provisions are self-implementing, even in the absence of the proposed rule.

Our estimate of the number of foreign registration and listing respondents is based on the PRIA. A number of foreign manufacturing establishments might not yet have registered with FDA if the drugs they manufacture are only indirectly imported or offered for import into the United States after undergoing further manufacture at another foreign establishment. These establishments thus would not have yet complied with section 510 of the FD&C Act, as amended by section 2511 of the PREVENT Pandemics Act. PRIA, section II.D.

If the proposed rule is finalized as proposed, we expect that some unregistered foreign firms would register. We estimate that about 25 foreign manufacturing establishments not currently registered with FDA might manufacture a drug subject to an approved application that is imported or offered for import into the United States after undergoing further manufacture at another foreign establishment. We estimate that about 1,600 foreign manufacturing establishments not currently registered with FDA might manufacture an over-the-counter (OTC) monograph drug that is

imported or offered for import into the United States after undergoing further manufacture at another foreign establishment. Some registrants may register more than one establishment. Based on the analysis in the PRIA, we estimate that 1,313 respondents would submit an initial foreign establishment registration for 1,625 currently unregistered foreign manufacturing establishments. PRIA, section II.D. Multiplying our current hour burden estimates approved in OMB control number 0910-0045 for registration (1.0 hour) and updates to registration (0.5 hour) by a factor of 1.8 to account for differences in English proficiency, we estimate that it will take a respondent 1.8 hours to submit an initial foreign establishment registration and 0.9 hour (54 minutes) to update a registration, as shown in Table 1.

We estimate that these respondent foreign establishments will submit 24,550 drug listings (550 for drugs subject to an approved application and 24,000 for OTC monograph drugs). PRIA, section II.D. Multiplying our current hour burden estimates approved in OMB control number 0910-0045 for listing (1.5 hour) and updates to a listing (0.75 hour) by a factor of 1.8 to account for differences in English proficiency, we estimate that it will take a respondent foreign establishment 2.7 hours to submit an initial listing and 1.35 hours to update a listing, as shown in Table 1.

In sum, if the proposed rule is finalized as proposed, we estimate an increase in burden of 5 responses and 3 hours annually for DME respondents and 52,350 responses and 103,819 hours annually for foreign manufacturing registration and listing respondents, for a total estimated increase in burden of 52,355 responses and 103,822 hours, annually. We will submit an information collection request under RIN 0910-AI94 for this proposed rule. Upon publication of a final rule, and subsequent OMB approval of the information collection, we expect to revise currently approved OMB Control No. 0910-0045 to consolidate the burden of the information collection associated with this rulemaking into that control number.

12b. Annualized Cost Burden Estimate

We assume an average pharmaceutical industry wage rate of $75.00 per hour to prepare and submit the information collection requirements under the proposed rule. When multiplied by the burden hours above, the cost to US-based respondents is estimated at $225.00 and the cost to unregistered foreign firms is estimated at $7,786,200.

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

There are no capital costs and operating and maintenance costs associated with this proposed collection of information.

14. Annualized Cost to the Federal Government

If the proposed rule is finalized, we estimate that FDA would incur one-time costs of ~$100,000 to update structured product labeling (SPL) submission schema, tools, and internal databases. PRIA, at section II.F.3. On an annualized basis, we estimate this cost to be $33,333.33 per year over 3 years ($100,000/3).

15. Explanation for Program Changes or Adjustments

This is a new information collection.

16. Plans for Tabulation and Publication and Project Time Schedule

The information collected will not be published or tabulated.

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

FDA will display the OMB expiration date as required by 5 CFR 1320.5.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.