4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 207

[Docket No. FDA-2025-N-6075]

RIN 0910-AI94

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing to amend the drug establishment registration and drug listing requirements with respect to establishments engaged in distributed manufacturing and foreign drug establishments. This action, if finalized, will provide a pathway for a distributed manufacturing establishment that manufactures drugs at multiple different physical locations to register as a single drug manufacturing establishment and align drug establishment registration and drug listing regulations applicable to foreign drug establishments with statutory changes made by the Preparing for and Responding to Existing Viruses, Emerging New Threats, and Pandemics Act (PREVENT Pandemics Act).

DATES: Either electronic or written comments on the proposed rule must be submitted by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Submit comments (including recommendations) on the collection of information under the Paperwork Reduction Act of 1995 by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system

will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted,

marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2025-N-6075 for "Drug Establishment Registration and Drug Listing Requirements for Establishments Engaged in Distributed Manufacturing and Certain Foreign Establishments." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents, the plain language

summary of the proposed rule of not more than 100 words as required by the "Providing Accountability Through Transparency Act," or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

Submit comments on the information collection under the Paperwork Reduction Act of 1995 to the Office of Management and Budget (OMB) at https://www.reginfo.gov/public/do/PRAMain. Find this particular information collection by selecting "Currently Under Review - Open for Public Comments" or by using the search function. The title of this proposed collection is "Drug Establishment Registration and Drug Listing Requirements for Establishments Engaged in Distributed Manufacturing and Certain Foreign Establishments (0910-NEW)."

FOR FURTHER INFORMATION CONTACT: *With regard to the proposed rule*: Ashley Boam, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 301-796-6341, ashley.boam@fda.hhs.gov.

With regard to the information collection: Anne Taylor, Office of Operations, Food and Drug Administration, Three White Flint North, 10A–12M, 11601 Landsdown St., North Bethesda, MD 20852, 240-402-5683, PRAStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

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I. Executive Summary

A. Purpose of the Proposed Rule

There are two purposes to this proposed rule. The first is to propose revisions to the drug establishment registration regulations to accommodate distributed manufacturing (DM) by providing drug manufacturers that engage in DM with flexibility in registration requirements. The second purpose is to propose updates to the drug establishment registration and drug listing regulations to incorporate clarifying changes to the statute made by section 2511 of the PREVENT Pandemics Act.

DM is a decentralized manufacturing strategy that uses advanced manufacturing technology. Under our proposal, a distributed manufacturing establishment (DME) uses a hub-and-spoke model in which the physical manufacturing activities are conducted at DM units (DMUs) that are located at one or more geographic locations ("spokes") under the oversight and control of a single quality unit, which has a management structure located at the DM "hub" and has implemented a unified pharmaceutical quality system (UPQS). The DMUs are equivalent in design and operation, manufacture the same drug(s), and can be added, removed, or relocated as needed to meet demand. In contrast, an establishment engaged in traditional manufacturing resides in one general physical location, and manufacturing is overseen by the manufacturer's quality unit located in the same general physical location.

Current registration regulations would require the hub, provided that it is engaged in manufacturing activities as defined by 21 CFR § 207.1, and each DMU within the DME to register as separate establishments even though they operate collectively as one establishment. These proposed regulations, if finalized, would provide a pathway for a DME to register as a single drug manufacturing establishment. The proposed regulations 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.

Section 2511 of the PREVENT Pandemics Act amended section 510(i) (21 U.S.C. 360(i)) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to expressly require the registration of foreign establishments engaged in the manufacturing, preparation, propagation, compounding, or processing of a drug that is imported or offered for import into the United States regardless of whether such drug undergoes further manufacture, preparation, propagation, compounding, or processing at a separate foreign establishment prior to being imported or offered for import into the United States. This amendment to section 510 of the FD&C Act also clarified that such foreign establishments must provide the drug listing information described in section 510(j) of

the FD&C Act with respect to such drugs. Submission of drug establishment registration and drug listing information on foreign establishments improves the Agency's visibility into the drug supply chain and enhances our ability to prevent the importation of drugs that do not comply with current good manufacturing practice (CGMP) requirements or are otherwise adulterated or misbranded.

B. Summary of the Major Provisions of the Proposed Rule

FDA proposes a registration pathway that is specific to DMEs. The proposed rule would modify certain definitions in part 207 (21 CFR part 207), including the definition of "establishment," and add new defined terms related to DM. The proposed regulations, if finalized, would enable a DME to register as a single establishment with the addition or removal of a DMU from a DME, or relocation of a mobile DMU, treated as an expedited update to the DME registration. The proposed rule includes requirements regarding initial registration and updates to registration that are similar to current requirements but consider aspects of the DM hub-and-spoke model that necessitate different regulations (e.g., timing of registration activities for DMEs with mobile DMUs).

Additionally, the Agency is proposing to amend the drug establishment registration requirements to clarify that the drug establishment registration requirements apply to each foreign establishment that manufactures, repacks, relabels, or salvages a drug that is imported or offered for import into the United States regardless of whether such drug undergoes further manufacture, preparation, propagation, compounding, or processing at a separate foreign establishment prior to being imported or offered for import into the United States. Similarly, the Agency is proposing to amend the drug listing requirements to clarify that the drug listing requirements apply with respect to any drug that a foreign establishment manufactures, repacks, relabels, or salvages for commercial distribution regardless of whether the drug undergoes further manufacture, preparation, propagation, compounding, or processing at a separate foreign establishment prior to being imported or offered for import into the United States.

C. Legal Authority

In conjunction with our general rulemaking authority in section 701(a) of the FD&C Act (21 U.S.C. 371(a)), this proposed rule is authorized by sections 201, 301, 501, 502, 505, 510 , 512, 704, 801, and 1003 of the FD&C Act (21 U.S.C. 321, 331, 351, 352, 355, 360, 360b, 374, 381, and 393), sections 351, 361, and 368 of the Public Health Service Act (PHS Act) (42 U.S.C. 262, 264, 271), and section 2511(b) of the PREVENT Pandemics Act.

D. Costs and Benefits

We quantify costs to drug manufacturers for reading and understanding the rule and to FDA for updating structured product labeling (SPL) submission schema, tools, and internal databases. Using a pre-statute baseline, we also estimate costs to unregistered foreign firms required to register and list with FDA, as we expect clarifying changes to statute made by section 2511 of the PREVENT Pandemics Act to increase compliance among covered foreign establishments. At a seven percent discount rate, estimated annualized net costs range from approximately $532,811 to $664,495, with a primary estimate of $583,958. At a three percent discount rate, the estimated annualized net costs range from approximately $482,472 to $606,839, with a primary estimate of $533,771. Unquantified benefits include greater visibility into the drug supply chain. We expect improved supply chain visibility to help support FDA's efforts with respect to preventing and mitigating drug shortages.

II. Abbreviations and Commonly Used Acronyms in This Document

Abbreviation/Acronym	What It Means
API	Active Pharmaceutical Ingredient
BLA	Biologics License Application
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
DM	Distributed Manufacturing
DME	Distributed Manufacturing Establishment
DMU	Distributed Manufacturing Unit
DUNS	Data Universal Numbering System
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA or Agency	Food and Drug Administration
FEI	FDA Establishment Identifier
FR	*Federal Register*

FRAME	Framework for Regulatory Advanced Manufacturing Evaluation
GPS	Global Positioning System
NDA	New Drug Application
OMB	Office of Management and Budget
PHS Act	Public Health Service Act
PRIA	Preliminary Regulatory Impact Analysis
PREVENT Pandemics Act	Preparing for and Responding to Existing Viruses, Emerging New Threats, and Pandemics Act
SPL	Structured Product Labeling
UFI	Unique Facility Identifier
UPQS	Unified Pharmaceutical Quality System

III. Background

A. Introduction

Advanced manufacturing is a term for an innovative pharmaceutical manufacturing technology or approach that has the potential to improve the reliability and robustness of the manufacturing process and supply chain and increase timely access to quality medicines for the American public. Advanced manufacturing can integrate novel technological approaches, use established techniques in an innovative way, or apply production methods in a new domain where there are no defined best practices or experience. Advanced manufacturing can potentially be used for new or currently marketed large or small molecule drugs. FDA's Center for Drug Evaluation and Research (CDER) established the Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) initiative in 2019 to ensure a regulatory framework to support the adoption of advanced manufacturing technologies that could bring benefits to patients (Ref. 1). This proposed rule is being issued, in part, under the FRAME initiative.

DM is a decentralized manufacturing strategy that uses advanced manufacturing technology. DM allows for greater flexibility in drug manufacturing by using a decentralized hub-and-spoke manufacturing model consisting of a single control site that has a management structure located at a centralized site, or "hub," and one or more DMUs at a different location from the hub ("spokes") that are equivalent in design and operations and can be added, removed,

or relocated as needed. In a hub-and-spoke model, the manufacturer can combine and collectively evaluate data from all DMUs to establish a validation strategy for a newly established manufacturing process. The knowledge and experience gained during the design stage from this collective data set could reduce the extent of validation activities that would be needed when adding subsequent DMUs to the DME or following relocation of an existing DMU. Data sets over the DMUs' operating lifetime may be further leveraged to support continued process verification. This agility in the validation strategy would be especially important for DMUs capable of mobility that are commissioned for their ability to move to new locations quickly to manufacture drugs in response to need (e.g., during an emergency). In addition to the knowledge that comes from having DMUs that are equivalent in design and operations, operating at the same time, another benefit to the hub-and-spoke model is that having DMUs in a diverse range of geographic areas can improve supply chain resiliency.

For the purposes of this proposed rule, we considered whether to permit manufacturers that use an alternative distributed manufacturing model to take advantage of the streamlined registration pathway for distributed manufacturing establishments. There are other models where a drug is made at multiple locations, and some may describe this as distributed manufacturing. However, it is unlikely that these models would be appropriate for the streamlined registration we propose for a number of reasons. For example, in section V.A.1, we discuss a model in which several different contract manufacturing organizations are hired to manufacture the same drug at different locations. In such an arrangement, the unaffiliated business entities would operate under different management that would not have the direct authority to manage another entity's quality system. In such circumstances, permitting a single, streamlined registration process to cover multiple corporate entities is unworkable; the registrant must be a single legal entity. Thus, in this example, each contract manufacturing organization would need to register and list separately under the existing regulations. In addition, based upon public input (see Section III.C of this proposed rule), we concluded that the approach described in this proposed

rule aligns well with the distributed manufacturing model industry is likely to adopt, and that would otherwise likely result in an additional registration burden on industry. We seek public comment on the benefits and burdens of applying this approach to other distributed manufacturing models.

DM is an alternative to traditional manufacturing and generally is envisioned to be utilized in circumstances where an agile approach to manufacturing is necessary or beneficial to meet patient needs for medicines, and when meeting such needs is either not possible or not ideal through traditional manufacturing. This proposed rule is being published, in part, to address the regulatory changes FDA has determined are appropriate for the registration of DMEs because of the differences between DM and traditional manufacturing.

This proposed rule is also being published to more explicitly address registration and listing requirements for foreign establishments that manufacture a drug that, as manufactured by such foreign establishment, is only distributed outside the United States (e.g., an active pharmaceutical ingredient (API) manufacturer that only distributes the API to finished product manufacturers outside of the United States) but is subsequently imported or offered for import into the United States after undergoing further processing at another foreign establishment. Many foreign establishments that manufacture drugs (including components of drugs such as APIs) [1] only for distribution to other foreign establishments have not registered or listed such drugs even if those drugs were subsequently imported or offered for import into the United States. As a result, this has impaired FDA's visibility into the drug supply chain with respect to drugs that are imported or offered for import into the United States (Ref. 2). Ensuring that such establishments are registered, and the drugs manufactured at such establishments are listed with FDA, as described in the proposed rule, will enhance our visibility into the drug supply chain

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[1] Pursuant to 21 CFR 207.13(f), manufacturers of certain components of drugs (i.e., harmless inactive ingredients) are not subject to the drug establishment registration requirements and that would not change if this proposed rule were finalized.

because establishment registration is the most direct method used by FDA to identify manufacturers of drugs. It is the primary source used for including establishments in FDA's drug establishment site selection model, which is used to prioritize manufacturing sites for routine quality-related surveillance inspections scheduled pursuant to section 510(h) of the FD&C Act. Additionally, these requirements will ensure that the registration and listing requirements applicable to drug manufacturers apply equally to foreign establishments as they do to domestic establishments.

B. Current Regulatory Framework and Need for the Regulation

Among other things, section 510 of the FD&C Act requires every person upon first engaging in the "manufacture, preparation, propagation, compounding, or processing" of a drug in any establishment that they own or operate, in any State, to register the establishment. Section 510 applies to domestic establishments and any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug that is imported or offered for import into the United States. The information FDA obtains about establishments through the registration process is used to fulfill several of its statutory mandates and public health and animal health objectives. The regulations codified in part 207 reflect FDA's implementation of section 510 of the FD&C Act.

In August 2016, FDA published the "Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, Including Drugs that are Regulated Under a Biologics License Application, and Animal Drugs" final rule (81 FR 60170) (2016 Registration and Listing Final Rule). The 2016 Registration and Listing Final Rule updated FDA's regulations governing drug establishment registration and drug listing requirements. These updated regulations, codified in part 207, apply to both human drugs, including biological products marketed under a biologics license application (BLA), and animal drugs, unless exempted from registration requirements under section 510(g) of the FD&C Act or 21 CFR § 207.13 or determined not to be applicable because the establishments are subject to registration

requirements set forth elsewhere in Title 21 of the CFR (i.e., blood establishments and establishments that solely manufacture medical devices).

1. Distributed Manufacturing Establishment Registration Requirements

Current drug registration requirements include requirements regarding (1) the entities who must register, and which establishments must be registered (§ 207.17); (2) initial registration for domestic and foreign establishments (§ 207.21 and § 207.25); and (3) updates to registration information on either an expedited or annual basis (§ 207.29).

The term "establishment" in § 207.1 is defined, in part, as "a place of business under one management at one general physical location." The preamble to the 2016 Registration and Listing Final Rule stated that "the longstanding language 'one general physical location,' generally restricts a single establishment to one street address or one or more contiguous plots of land" (81 FR 60170 at 60178); and "under the final rule's definition of 'establishment,' two establishments located 5 miles apart would not qualify as being at 'one general physical location' and would therefore require two separate registrations. Each establishment would be associated with its own [unique facility identifier] and establishment registration number" (81 FR 60170 at 60189).

This definition has been appropriate for establishments utilizing traditional manufacturing approaches that consist of manufacturing facilities under one management at one general physical location but may not be suitable for DMEs. A DME similarly operates as a single establishment under one management but is not located at one general physical location. With the current definition of establishment, a DME that follows a hub-and-spoke model where the hub and each DMU spoke reside in more than one general physical location, and where a DMU may further move to new locations, would be required to submit a separate registration for (1) each DMU that is manufacturing drugs at a different location; (2) the hub, provided it is engaged in manufacturing activities as defined in § 207.1; and (3) any DMU subsequently added at or moved to a new location.

The requirement under existing regulations to submit multiple, separate registrations for a single DME would be unnecessarily burdensome for industry and could pose a barrier to the adoption and implementation of DM. For FDA, it could limit our understanding of connections between the hub and its DMUs and our awareness of manufacturing operations that are utilizing a UPQS to direct, monitor, and control the manufacture of drugs to ensure product quality at the distributed manufacturing establishment, including ensuring that all distributed manufacturing units within the distributed manufacturing establishment at any location are and remain equivalent in design and operation.

Additionally, information currently required for registration and expedited updates to registration would need to be expanded to include important DM-specific details, such as the number and location of individual DMUs, which could reside domestically or across multiple different countries and be added and removed over time in response to demand. Similarly, changes to the timelines for the submission of certain information would need to be more tailored to DM, in particular for mobile DMUs, which can relocate, possibly frequently.

We are undertaking this rulemaking to establish a registration pathway appropriate for DMEs. 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 responsibilities.

2. Foreign Establishment Registration and Drug Listing Requirements

Nothing in the preamble to the 2016 Registration and Listing Final Rule nor the codified regulations directly addressed whether the registration and listing requirements applied to foreign establishments that manufactured a drug that was only distributed outside the United States (e.g., API manufacturer that only distributes the API to finished product manufacturers outside of the United States) but is subsequently imported or offered for import into the United States after undergoing further processing at another foreign establishment. However, the "Requirements for Foreign and Domestic Establishment Registration and Listing

for Human Drugs, Including Drugs That Are Regulated Under a Biologics License Application, and Animal Drugs, Final Regulatory Impact Analysis, Final Regulatory Flexibility Analysis, Unfunded Mandates Reform Act Analysis" (2016 Registration and Listing FRIA) that accompanied the publication of the 2016 Registration and Listing Final Rule appeared to address this issue. Specifically, the 2016 Registration and Listing FRIA noted that a foreign API manufacturer that only distributes an API outside of the United States is not required to register even if the finished product manufactured from the API is eventually imported into the United States. At that time, the majority (approximately 65 percent) of establishments required to register and list were in the United States.

However, since the publication of the 2016 Registration and Listing Final Rule, the percentage of foreign establishments required to register has increased, and as of October 2024, nearly 60 percent of registered drug establishments are outside of the United States (Ref. 3, page 4). The number of foreign establishments that manufacture APIs used in finished products imported into the United States but do not register because they only distribute the API outside of the United States has also likely grown since the publication of the 2016 Registration and Listing Final Rule. The lack of registration and listing among such entities has hindered FDA oversight over a growing sector of the supply chain because FDA may not be aware of these unregistered establishments. Therefore, they would not be considered when FDA is prioritizing surveillance inspections which are a critical tool used in safeguarding the public from harmful, unsafe, and ineffective products.

In December 2022, Congress passed, and the President signed into law, the PREVENT Pandemics Act. 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. This proposed rule is intended to update the drug establishment registration and listing requirements for foreign establishments to align the regulations with the changes made to section 510 of the FD&C Act.

Updating the registration and listing regulations to be consistent with these clarifying changes to section 510 of the FD&C Act will eliminate any perceived inconsistencies between the statutory requirements in section 510 of the FD&C Act and the regulatory requirements in part 207. Eliminating any such inconsistency should increase compliance with the registration and listing requirements and thus increase FDA's visibility into this area of the drug supply chain. This increased visibility will then enhance FDA's efforts to prevent adulterated or misbranded drugs from reaching patients and consumers.

C. History of the Rulemaking

In developing the part of this proposed rule regarding DMEs, FDA published a discussion paper (Ref. 4) on October 14, 2022, entitled "Distributed Manufacturing and Point-of-Care Manufacturing of Drugs Discussion Paper" and opened a docket for public comment (FDA-2022-N-2316). The paper posed questions related to the technical aspects of DM technologies, compliance with current regulations such as requirements related to CGMP and regulatory submissions, and terminology to inform future policy development. FDA received over 25 comments through the docket from industry groups, individual companies in the pharmaceutical and related sectors, and private citizens. Commenters sought clarity on how existing regulations (e.g., establishment registration) apply to DM technology; requested assurance that regulations and policies are compatible with DM strategies; emphasized the importance of a centralized pharmaceutical quality system; highlighted the need to reduce burden associated with having

multiple manufacturing establishments at different locations and the possibility of location changes; advocated for risk-based approaches to inspections that recognize the unique capabilities and controls of DM units; and called for international harmonization to facilitate global adoption of DM technologies. Commenter feedback was incorporated in FDA's report entitled "Distributed Manufacturing of Drugs: Stakeholder Feedback and Action Plan" (November 2023, Ref. 5). FDA also co-sponsored a public workshop on November 14-16, 2022 (Ref. 6), to discuss important topics for the development and implementation of DM technologies with interested stakeholders from industry and academia. In developing this proposed rule, FDA considered the public feedback that a different, less burdensome approach for registration and listing may be needed for a DM establishment that might consist of multiple DM units, possibly mobile, overseen by a single quality unity that has implemented a unified pharmaceutical quality system. We are continuing to consider the other comments not related to establishment registration, which are outside the scope of this rule.

IV. Legal Authority

We are issuing this proposed rule under sections 201, 301, 501, 502, 505, 510, 512, 701, 704, 801, 1003 of the FD&C Act (21 U.S.C. 321, 331, 351, 352, 355, 360, 360b, 371a, 374, 381, and 393) and sections 351, 361, and 368 of the PHS Act (42 U.S.C. 262, 264, 271). Section 510(c) of the FD&C Act requires every person upon first engaging in the manufacture, preparation, propagation, compounding, or processing of a drug to immediately register with the Secretary, among other things, his name, place of business, and the establishment. The provisions in section 510(b) and (d) of the FD&C Act require annual registration and registration of additional establishments, respectively. The information specified in this proposal would help us identify who is manufacturing drugs through a DMU(s) and where those operations are being performed. Section 510(i)(5) expressly requires the registration of foreign establishments engaged in the manufacturing, preparation, propagation, compounding, or processing of a drug that is imported or offered for import into the United States regardless of whether such drug

undergoes further manufacture, preparation, propagation, compounding, or processing at a separate foreign establishment prior to being imported or offered for import into the United States. These provisions, together with section 701(a) of the FD&C Act (among others), authorize us to require the submission of the registration and drug listing information specified in the proposal. The failure to register or list is a prohibited act under section 301(p) of the FD&C Act and the failure to do either renders a drug misbranded under section 502(o) of the FD&C Act.

V. Description of the Proposed Rule

We are proposing to revise part 207 to: (1) provide a pathway for a DME, as defined in this proposed rule, which performs manufacturing activities at one or more physical locations to register as a single drug manufacturing establishment, and (2) clarify the applicability of the establishment registration and drug listing requirements to foreign drug manufacturing establishments that do not directly import or offer for import drugs into the United States, but are still involved in the manufacture of drugs that are imported or offered for import into the United States.

A. Distributed Manufacturing Establishment Registration

We propose to revise part 207 to include DME-specific registration requirements that are better tailored to the hub-and-spoke model of DM than the current registration requirements. FDA proposes to create a registration pathway to enable a DME with operations at multiple locations to register as a single establishment by modifying certain definitions in part 207; adding new definitions for DM; revising and expanding requirements regarding the timing and information submitted for initial registration and subsequent updates to registration; and providing requirements specific to DMEs comprised of DMUs capable of mobility.

1. Definitions

To accommodate DM-specific registration requirements, we propose revisions to the definitions for "establishment," "domestic," and "foreign" in § 207.1. Proposed § 207.1 also

adds new definitions for "distributed manufacturing establishment," "distributed manufacturing hub," and "distributed manufacturing unit." Each of these revised and new definitions are described in turn below. The new definitions include references to several other terms that are currently not defined in FDA regulations, such as "equivalent" and "unified pharmaceutical quality system," and we are seeking comment on whether any of these other terms should be formally defined in the final rule and, if so, how they should be defined.

FDA proposes to revise the definition of "establishment" to include DMEs. FDA currently defines the term "establishment" to mean a place of business under one management at one general physical location and lists types of establishments that are included in this definition. The proposed revision would expressly include DMEs as a type of establishment, even though each DMU within a DME generally will operate at different locations, will not be at the same general physical location as the DM hub, and might further relocate.

FDA proposes to separately define the term "distributed manufacturing establishment" to distinguish a DME from an establishment engaged in traditional manufacturing. An establishment engaged in traditional manufacturing manufactures, prepares, propagates, compounds, or processes drug(s) at one general physical location with the manufacturer's quality unit responsible for oversight typically being entirely present at that same location. In contrast we propose to define a DME as an establishment that manufactures, prepares, propagates, compounds, or processes drug(s) utilizing a manufacturing strategy designed to be decentralized (i.e., a hub-and-spoke model), where DMUs that are equivalent in design and operations are at different locations (the DMUs are the "spokes") and manufacture the same drug(s) under the oversight and control of a single quality unit, which has a management structure located at the DM "hub" and has implemented a UPQS.

Additionally, the proposed definition of DME specifies that the hub and all associated DMUs collectively (a) operate under one management pursuant to a manufacturing strategy designed to be decentralized, and (b) were subject to a preapproval inspection because at least

one drug in each profile class manufactured by the DME is manufactured in accordance with an approved application that, at the time of an original submission or postapproval submission, describes the use of a decentralized manufacturing strategy. The relevant applications are new drug applications (NDAs) submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act (including NDAs described in section 505(b)(2) of the Act); abbreviated new drug applications (ANDAs) submitted and approved under section 505(j) of the FD&C Act; new animal drug applications (NADAs) submitted under section 512(b)(1) and approved under section 512(c)(1) of the FD&C Act; abbreviated new animal drug applications (ANADAs) submitted under section 512(b)(2) and approved under section 512(c)(2) of the FD&C Act; or biologics license applications (BLAs) submitted and approved under section 351(a) or (k) of the PHS Act.

The requirement that the DM hub and DMUs operate under one management, which is also an expectation for establishments engaged in traditional manufacturing, means that a single business entity (i.e., the registrant) manages the DME in its entirety. This requires quality oversight for the DME to be executed by one business entity that has the authority and responsibility for ensuring CGMP requirements are met and does so via the UPQS. By implementing the UPQS, the registrant ensures that the quality unit provides uniform quality oversight and control across the DME. The Agency intends to provide additional guidance on compliance with CGMP requirements as applied to distributed manufacturing.

The proposed definition of DME would not permit an arrangement where several different contract manufacturing organizations are hired to each operate a DMU to manufacture the same drug(s) at multiple locations. This is because, when unaffiliated business entities are involved, there are potentially competing quality systems, which can make it difficult to ensure equivalency in design and operations is maintained across DMUs. Even if each of the DMUs were of equivalent design and were intended to have equivalent operations, each DMU would be under different management and therefore, operating under the oversight and control of

different quality units, which by their very nature would not have implemented a UPQS. The proposed registration approach for DMEs would not be available to relabelers, repackers, or salvagers that are third parties to the applicant and the manufacturer and do not operate under the ownership or control of the manufacturer. They would not meet the requirement of having a UPQS in order to be considered a DME.

Under our proposal, a DME must have been subject to a preapproval inspection in connection with an application that, at the time of an original or postapproval submission, describes the use of a decentralized manufacturing strategy for at least one drug in each profile class manufactured by the DME. Furthermore, our proposal allows for multiple profile classes to be manufactured at a single DME, provided that the DME meets the requirement regarding being subject to a preapproval inspection for each profile class of drug manufactured at the DME. Profile class of a drug refers to the categorization of different processing conditions and product types. For example, immediate-release, delayed-release, and extended-release solid oral dosage forms would be different profile classes of drugs. Profile classes are described in FDA's Investigations Operations Manual (Ref. 7) and are used by FDA for inspection planning and to aid decision-making. When deciding whether a new product-specific inspection, such as a preapproval inspection, is needed, FDA uses profile classes to assist in determining whether a previous FDA inspection of an establishment has already covered similar manufacturing operations, such that those inspectional findings can be applied to new, but similar, products and processes. For DM, the opportunity during a preapproval inspection to review the effectiveness of the UPQS is especially important to confirm that the UPQS is capable of managing changes in manufacturing operations to ensure equivalency in design and operation across DMUs.

FDA is proposing to permit DMEs to manufacture certain products marketed without an approved application (e.g., over-the-counter (OTC) monograph drugs) in addition to those marketed pursuant to an approved application. Specifically, an establishment registered as a

DME may manufacture drugs not subject to an approved application, so long as each such non-application product is of the same profile class as one or more drugs manufactured by the DME pursuant to an approved application that describes the use of a decentralized manufacturing strategy. Thus, an approval of an application to manufacture a drug, by the DME, using a decentralized manufacturing strategy can provide assurance that the DME is prepared to perform CGMP-compliant manufacturing activities for a non-application product that is similar to (i.e., of the same profile class as) an application product manufactured by the DME. We note that if an establishment's manufacture of an API using a decentralized manufacturing strategy was described in a drug master file that is appropriately referenced in an approved application, that establishment would have been subject to a preapproval inspection, and for purposes of registration and listing, may be considered a DME for the manufacture of other APIs classified under the same FDA profile class, even if those other APIs are further processed into non-application drug products.

In contrast to traditional manufacturing, in which drug products are manufactured at a single physical location, distributed manufacturing needs to be decentralized, taking place at more than one location. Therefore, a DME is also defined as including either at least one DMU capable of mobility (i.e., capable of manufacturing in multiple locations) or at least two DMUs if none of the DMUs are capable of mobility. A DMU capable of mobility refers to a unit that can be transported readily from one location to another or is able to move itself from one location to another, and is therefore capable of manufacturing at multiple locations on its own. Therefore, manufacturing can be decentralized using a single DMU capable of mobility so long as, after it moves, it remains equivalent in design and operations to its design and operations at its previous location. The complexity of the DMU (the external structure and internal manufacturing line) coupled with the complexity of relocation (transport, arrival, and set-up at the destination) introduces multiple, independent factors (e.g., climate, utilities) that could impact its ability to have equivalent design and operations at the new location. Therefore, the

equivalency of that unit at the new location would need to be evaluated and confirmed prior to manufacturing at the new location and through continued validation and monitoring, even though it is the same DMU.

FDA also proposes to define "distributed manufacturing unit" and "distributed manufacturing hub." Defining these terms clarifies the role of each of these parts of a DME and is necessary because certain registration requirements may be applicable only to a particular part of the DME.

We propose to define a "distributed manufacturing unit" to mean a physical unit engaged in the manufacture, preparation, propagation, compounding, or processing of drug(s) that is generally deployed, or put into effect, at a separate location from the DM hub and that may further move from one general physical location to another if the unit is capable of mobility. We note that a hub would not be considered a DMU if it only serves as the primary location of the quality unit responsible for implementing the UPQS and is not otherwise performing manufacturing activities other than those related to implementing the UPQS. See additional discussion in the section on the definition of the DM hub.

All DMUs within a given DME would be required to be of equivalent design and operation regardless of the location of the DMU deployed and would be expected to maintain this equivalency of design and operations over time. The term "equivalent" is not intended to mean identical, which is a stricter standard. Certain elements of a DMU can be equivalent but not identical. For example, if a manufacturer adds a new DMU to a DME that had been manufacturing a drug using a piece of equipment that has been discontinued, a newer model capable of meeting the same design and operation criteria to be able to produce the same drug according to its specifications may be considered equivalent and acceptable to use in the newly added DMU. Establishing and maintaining this equivalency ensures that each DMU that manufactures the same drug(s) and meets the same quality standards and specifications.

Complying with CGMP requirements and ensuring that each equivalent DMU continues to operate in a state of control is important for maintaining equivalency across DMUs. Therefore, the Agency intends to provide additional details in an Agency guidance on CGMP considerations for DM. This guidance will assist manufacturers in addressing the complexities associated with DM when complying with FDA's CGMP requirements (e.g., equivalency, control procedures implemented under a UPQS, and mobile units). .

We propose to define a "distributed manufacturing hub" to mean the place of business at one general physical location that is the primary location of the quality unit responsible for implementing the UPQS to direct, monitor, and control the manufacture of drugs to ensure product quality at the DME, including ensuring that all DMUs are and remain equivalent in design and operation. The proposed definition for the hub does not preclude the hub from performing other manufacturing activities in addition to activities related to the UPQS. If a DM hub manufactures the same drug(s) as the other DMUs in the DME and is equivalent in design and operation to the other DMUs, then the hub would also be considered a DMU.

One function of the UPQS is to provide the structure to ensure DMUs are, and remain over time, equivalent in design and operations. Under a UPQS, the personnel in the manufacturer's quality unit develop the policies and procedures that govern manufacturing operations for the entire DME; determine appropriate staffing and the personnel reporting structure for the entire DME; and conduct the overall lifecycle management for all DMUs.

The proposed definition of DM hub differentiates the DM hub from traditional sites that may have centralized certain quality oversight activities but have not implemented a UPQS. For example, a company may decide to manufacture the same drug using the same processes at several of its existing establishments at various locations and consolidate certain quality responsibilities of several establishments (e.g., complaint coordination, global procedures) at a central site such as company headquarters.

FDA also proposes to revise the definitions of "domestic" and "foreign" in 21 CFR 207.1 to include "distributed manufacturing hub" and "distributed manufacturing unit" as terms that can be characterized as either domestic or foreign, depending on location.

FDA seeks comment on whether there are other terms, including those that are used in this proposed rule, that the Agency should define or clarify in part 207 and how such a term should be defined.

2. Who Must Register

Establishment registration requirements apply to any manufacturer subject to section 510 of the FD&C Act and the implementing regulations in part 207 who is manufacturing, repacking, or relabeling a drug, or an animal feed bearing or containing a new animal drug for commercial distribution within the United States and/or for import into the United States, which would include entities involved in such activities using DM. Proposed § 207.17(b) creates a separate registration requirement for DMEs. Although this new proposed requirement is similar to the requirement under § 207.17(a), a separate provision was necessary because of certain aspects specific to DMEs. Specifically, it clarifies that in determining whether a DME is required to register, we do not evaluate whether the entire DME is domestic or foreign, but rather we focus on whether the components of the DME (i.e., the DM hub or the DMU(s)) are domestic or foreign. As proposed, the registration requirements are triggered if the DME includes a domestic hub or DMU, or a foreign hub or DMU that manufactures a drug, or an animal feed bearing or containing a new animal drug that is imported or offered for import into the United States regardless of whether the drug, or animal feed bearing or containing a new animal drug undergoes further manufacture, preparation, propagation, compounding, or processing at a separate foreign establishment prior to being imported or offered for import into the United States. We note that proposed § 207.17(b) includes the same language regarding foreign establishments that FDA is proposing to add to current § 207.17(a) consistent with section 2511 of the PREVENT Pandemics Act (see section V.B of this document).

Section 510(g) and § 207.13 include certain exemptions to the drug establishment registration requirements. Generally, FDA expects that many of the exemptions in section 510(g) and § 207.13 would not apply to an establishment engaged in DM because engaging in the distributed manufacturing of a drug for commercial distribution would, in and of itself, be an activity that would require the establishment to register under § 207.17 (see § 207.13(l)(3)). However, to be consistent with § 207.17(a), and to allow the possibility that an establishment engaged in DM may still be exempt from establishment registration under § 207.13, (e.g., it is using DM to manufacture a drug used in research, teaching, or chemical analysis and not for sale), FDA included language in proposed § 207.17(b) subjecting the registration requirements to the exemptions in section 510(g) and § 207.13.

3. When Must Initial Registration Information Be Provided?

FDA proposes separate initial registration requirements for DMEs that generally track with current requirements under § 207.21 but are tailored to the hub-and-spoke model of a DME. Proposed § 207.21(b)(1) would require a DME to register no later than 5 calendar days after the first domestic DMU begins to manufacture a drug for commercial distribution, or before a drug manufactured at any foreign DMU is imported or offered for import into the United States, whichever of the two occurs first. This requirement addresses the possibility that a DME may include both domestic and foreign DMUs.

Proposed § 207.21(b)(2) addresses how registrants can fulfill the initial registration requirement for a DME when the DM hub is located at, and operated as part of, a currently registered establishment. In this instance, the initial establishment registration requirement under § 207.21 has already been met, so registering the DME would be handled as an update to the existing establishment registration and is included as such in proposed § 207.21(b)(1). Permitting a facility to be both a "traditional" establishment and a DM hub under a single registration is practical because the facility is at the same address and owned by the same company, but with different business operations depending on establishment type. Furthermore,

certain items such as standard operating procedures (e.g., how to conduct an investigation) would likely apply to both establishment types.

Although registering a DME in this situation is managed as a registration update, it is effectively a new registration for the DME. Therefore, FDA proposes that the timeline for initial registration, which is 5 calendar days, rather than the 30-day timeline required for an expedited update, apply in this instance as the timeline for updating the existing registration. FDA believes that when the registration update is for purposes of notifying FDA that the existing registered establishment will serve as the hub of a DME, the 5-calendar day timeframe would be more appropriate.

4. Information Required for Registration

FDA proposes to create a new paragraph (b) in § 207.25 that would list the type of information required when registering DMEs. 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.

Proposed § 207.25(b) would require registrants to provide the same basic establishment information and contact details currently required when registering establishments that are not DMEs:

- Name of the owner or operator of the DME; the name of each partner; the name of each corporate officer and director; and the place of incorporation, as applicable (see proposed § 207.25(b)(1))
- All name(s) of the DME by which it is known (see proposed § 207.25(b)(3))
- Registration number of the DME (see proposed § 207.25(b)(4))
- UFI of the DME (see proposed § 207.25(b)(5)); and
- Name, mailing address, telephone number, and email address of the official contact for the DME (see proposed § 207.25(b)(8)).

Pursuant to Agency guidance (Ref. 8), the UFI required by current § 207.25(e) is Dun & Bradstreet's Data Universal Numbering System (DUNS) number (Ref. 8), a unique numeric identifier for a specific business entity. Similarly, the registration number required by current § 207.25(d) for each establishment is described in guidance as the FDA Establishment Identifier (FEI) and is assigned by the FDA to identify establishments associated with FDA-regulated products. We note that FDA is not proposing to change the current numbering system utilized for the UFI, nor are we proposing changes to the FEI. We are, however, proposing a new approach for the application of the UFI and FEI as it relates to a DME. We propose assigning both the UFI and FEI to the DM hub because the DM hub is the central place of business that occupies one general physical location and is under the same ownership and control as the DMUs. In addition, FDA is proposing to require a unique identifier for each DMU. This unique identifier (e.g., a sub-FEI number) will be assigned by FDA and is intended to both identify each DMU as an individual unit and indicate its association with a particular hub (see section V.A.4 of this document). The registrant would also be required to meet the following provisions that either modify an existing requirement to tailor it to DMEs, or have been newly added because it is information unique to DMEs:

- Name, address, and telephone number of the DM hub (see proposed § 207.25(b)(2)). This proposed requirement specifies the DM hub because the hub must be stationary, residing at one general physical location. A DM establishment itself does not have a single address given that the hub and associated units reside in different physical locations.
- Unit identifier for each DMU of a DME (see proposed § 207.25(b)(6)(i)) that is assigned by FDA. The unit identifier is intended to distinguish the DMUs from one another. Each unit identifier would be unique, but a portion of the identifier would be common across all DMUs of a DME to indicate that they are associated with a particular hub to form the DME. Because units must be equivalent, the unit identifier is important for

traceability and data integrity purposes. It enables manufacturers and FDA to verify from which DMU manufacturing data is being generated.

- Location of each DMU of a DME (proposed § 207.25(b)(6)(ii)). The registrant must provide the location of each unit as a physical address or global positioning system (GPS) coordinates.
- Types of operations performed at the DME (see proposed § 207.25(b)(7)). This proposed requirement would require registrants to distinguish between the manufacturing operations performed at the DMUs and at the DM hub. The current list of business operations for use in establishment registration can be found on the FDA's Structured Product Labeling Resources website[2] to which DM-specific business operations will be added prior to implementing a final rule. This proposed provision recognizes the different roles of the DM hub compared to the DMUs. The centralized quality unit primarily located at the DM hub has the responsibility for directing, monitoring, and applying the necessary control procedures to the final product or to any part of the process, and could also be involved in manufacturing activities, including activities that differ from those taking place in the DMUs (e.g., if certain testing is performed at the hub but not at the DMUs).
- Information on the U.S. Agent and importers (see proposed §§ 207.25(b)(9) and 207.25(b)(10)). FDA proposes to require the same types of information on U.S. agents and importers currently required under § 207.25(h) for foreign establishments that are not DMEs. However, the proposed requirements are tailored to DMEs, which can have a foreign DM hub and/or foreign DMUs. For DMEs with a foreign DM hub, the registrant must provide the name, mailing address, telephone number, and email address

[2] See https://www.fda.gov/industry/structured-product-labeling-resources/business-operation

of the U.S. Agent (see proposed § 207.25(b)(9)(i)) and each entity involved in the importation of any drug to the United States from the foreign DM hub and any foreign DMUs that are part of the DME (see proposed § 207.25(b)(9)(ii) and (iii)). For DMEs with a domestic DM hub and at least one foreign DMU, proposed § 207.25(b)(10)(i) and (ii) require the name, mailing address, telephone number, and email address of each entity involved in the importation of any drug to the United States from any of the foreign DMUs that are part of the DME. We note that in this instance, the domestic distributed manufacturing hub could serve as the importer in the United States of drugs manufactured at one of the foreign DMUs, and the foreign DMU could serve as the person who imports or offers for import such drug to the United States.

5. Reviewing and Updating Registration Information

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 DMEs would apply to DMEs, as well as new categories of expedited updates tailored to DMEs with DMUs capable of moving or being moved.

The following list of changes that FDA proposes for submission 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:

- Changing the name of a DME. The corresponding provision in current § 207.29(a)(2) requires registrants to submit a change in name or physical address of an establishment as an expedited update. For a DME, however, there is no single address. There are multiple different locations for the various parts of the DME. For this reason, FDA proposes to have separate provisions for a change to the name of the DME (see proposed § 207.2(b)(3)(ii)) and a change in the location of the DM hub (see proposed §

207.29(b)(3)(iii)). Location changes for the units are addressed in proposed § 207.29(b)(4).

- Changing the physical address of the DM hub (see proposed § 207.29(b)(3)(iii) and discussion in previous bullet).
- Closing or selling a distributed manufacturing establishment. This proposed requirement in § 207.29(b)(3)(iv) is identical to § 207.29(a)(1).
- Changing the name, mailing address, telephone number, or email address of the official contact or the United States agent. This proposed requirement in § 207.29(b)(3)(v) is identical to § 207.29(a)(3).

In addition, FDA proposes the following information, specific to DMEs, be submitted on an expedited basis:

- Initial registration of a DME in which the hub is located at and operated as part of a currently registered establishment (see proposed § 207.29(b)(1)). This proposed provision would require registrants to update the existing registration on the 5-day timeline required under proposed § 207.21(b)(1) (see discussion in section V.A.3 of this document) and with the information required under proposed § 207.25(b) (see discussion in section V.A.4 of this document).
- Addition of a new DMU to an already registered DME (see proposed § 207.29(b)(2)). This proposed provision would require registrants to update the existing registration when a new DMU is added to a DME on a timeline determined by whether the unit is domestic or foreign. Similar to the timeline for initial registration, for a domestic DMU, the update must be provided 5 calendar days after the unit begins to manufacture a drug or an animal feed bearing or containing a new animal drug for commercial distribution; and for a foreign DMU, before a drug or an animal feed bearing or containing a new animal drug manufactured at a foreign DMU is imported or offered for import into the United States.

- Removing a DMU from a DME. In addition to voluntary removal of a DMU from a DME, a registrant must remove a DMU from a DME when the registrant discontinues manufacturing at the DMU or when the DMU no longer remains equivalent in design and operations, and the registrant has not taken steps to return the DMU to being equivalent in design and operations (see proposed § 207.29(b)(3)(i)). We note if a DMU fails to remain equivalent in design and operations to the other DMUs in the DME, and the registrant fails to take action to return the DMU to being equivalent in design and operations, the establishment may no longer meet the definition of DME in § 207.1. Furthermore, an establishment registered as a DME that does not meet the definition of a DME in § 207.1 would not be duly registered, and any drugs manufactured at such an establishment would be deemed to be misbranded pursuant to section 502(o) of the FD&C Act.
- Relocation of a mobile unit (see proposed § 207.29(b)(4)(i) and (ii)). This proposed provision would require registrants to notify FDA in advance when a DMU moves to a new location. The proposed timeline for this notification would differ depending on whether the destination is a location in the United States or a location in a foreign country. When a DMU moves within the United States or to a U.S. location from a foreign country, the registrant must provide FDA notification at least 30 calendar days prior to the relocation (see proposed § 207.29(b)(4)(i)(1)), whereas a move to any foreign country or to a different location within the same foreign would require at least 120 calendar days advance notice (see proposed § 207.29(b)(4)(i)(2)). The proposed 30 and 120 calendar day timelines reflect the amount of time needed to prepare for a domestic versus foreign inspection, if needed. The longer timeframe proposed for a DMU moving within or to a foreign country reflects the additional time needed for activities such as securing visas, country clearances, and translators to conduct a foreign inspection. The Agency specifically requests comment on the appropriateness of the 30-

day and 120-day timelines. In the notification, the registrant would be required to provide the unit identifier of the mobile unit; the departure and destination locations (physical address or GPS coordinates) and departure and arrival dates, and anticipated date for the resumption of manufacturing operations at the new location (see proposed § 207.29(b)(4)(ii)). Upon arrival at the destination, the registrant must update the registration once manufacturing has commenced (see proposed § 207.29(b)(4)(iii)). This expedited update must be provided no later than 5 calendar days after a domestic DMU begins manufacturing activities, or before importing drug manufactured at a foreign DMU into the United States.

In limited cases, such notice may not be possible because relocation was not reasonably anticipated in advance of the specified timeline. FDA requests comment on the specific circumstances where providing such advance notice would not be feasible and in those situations, when would a registrant first be able to notify the Agency.

B. Foreign Establishment Registration and Listing Requirements

We are proposing to amend § 207.17 and § 207.41. The proposed rule would eliminate any perceived inconsistencies between section 510 of the FD&C Act (as amended by the PREVENT Pandemics Act) and 21 CFR 207. These amendments will clarify that the drug establishment registration and drug listing requirements apply to foreign establishments engaged in the manufacture, preparation, propagation, compounding, or processing of a drug that is imported or offered for import into the United States, even if such drug undergoes further manufacture, preparation, propagation, compounding, or processing at another institution outside of the United States before it is imported or offered for import into the United States.

To ensure part 207 is aligned with the requirements in section 510 (as amended by section 2511 of the PREVENT Pandemics Act), we are proposing to amend §§ 207.17 and 207.41. Specifically, we are proposing to move the language currently in § 207.17(a) that relates to the registration requirements for domestic establishments into a new paragraph (1)

under subsection (a) and to move the language currently in subsection (a) that relates to the registration requirements of foreign establishments into a new paragraph (2) of subsection (a). Additionally, we are proposing to add the following language to the end of the first sentence of the new subparagraph (2): "regardless of whether the drug, or animal feed bearing or containing a new animal drug undergoes further manufacture, preparation, propagation, compounding or processing at a separate foreign establishment prior to being imported or offered for import into the United States." This proposed additional language mirrors the language added to section 510(i)(5) pursuant to section 2511 of the PREVENT Pandemics Act.

Proposed § 207.17(a)(2), if finalized, would clarify that the registration requirements apply to an establishment that manufactures, prepares, propagates, compounds, or processes a drug outside of the United States even if such drug is only distributed outside the United States if such drug is used in the manufacture, preparation, propagation, compounding, or processing of a drug that is ultimately imported or offered for import into the United States. For example, if these changes to 207.17 are finalized as proposed, the establishment registration requirements in part 207 would be aligned with the requirement in section 510(i) of the FD&C Act that the owner or operator of an establishment outside of the United States that manufactures an API and only distributes that API to finished product manufacturers that are also outside of the United States would be required to register the API manufacturing establishment, provided that the finished product is imported or offered for import into the United States.

To align the requirements in part 207 with the clarifying changes to section 510(i) of the FD&C Act made by section 2511 of the PREVENT Pandemics Act, we are also proposing to amend § 207.41. Specifically, we are proposing to add a new subsection (d) to clarify that the registrant must comply with drug listing requirements described in subsections (a), (b), and (c) with respect to a drug that it manufactures, repacks, relabels, or salvages for commercial distribution at a foreign establishment, regardless of whether such drug undergoes further

manufacture, preparation, propagation, compounding, or processing at a separate establishment outside the United States before being imported or offered for import into the United States.

As amended, proposed § 207.41(d) would clarify that the drug listing requirements apply to drugs that are manufactured, repacked, relabeled, or salvaged for commercial distribution at an establishment outside the United States if such drug is used in the manufacture, preparation, propagation, compounding or processing of a drug that is ultimately imported or offered for import into the United States. For example, if these changes to § 207.41 are finalized as proposed, the drug listing requirements in part 207 would align with the drug listing requirements in section 510 of the FD&C Act (as amended by section 2511 of the PREVENT Pandemics Act) such that an establishment outside of the United States that manufactures an API and only distributes that API to finished product manufacturers that are also outside of the United States, the owner or operator of the API manufacturer would be required to list that API in accordance with § 207.41, provided that the finished product is imported or offered for import into the United States.

We recognize that some foreign establishments that are required to register may not know how their customers intend to use the drug they distribute and thus may not know that they are required to register their establishment or list certain drugs that they manufacture. However, if such a foreign establishment fails to register, any drug that is imported or offered for import that was manufactured, prepared, propagated, compounded, or processed at such establishment would be considered misbranded pursuant to section 502(o) of the FD&C Act. A drug would be considered to have been manufactured, prepared, propagated, compounded, or processed at such an establishment if the drug manufactured at that establishment was a component of a drug that was imported or offered for import into the United States.

For example, if a foreign establishment manufactures an API and that API is distributed to another foreign establishment and the second foreign establishment uses the API to manufacture a finished product that is imported or offered for import into the United States, the

API would be considered to be a drug that was imported or offered for import into the United States. Therefore, both the API manufacturer and the finished product manufacturer would be required to register their respective establishments, and the API manufacturer would be required to list the API, and the finished product manufacturer would be required to list the finished product.[3] If either establishment is not appropriately registered and the API and finished product are not appropriately listed, both the finished product and the API will be considered misbranded.

Therefore, in this scenario, in order for the finished product manufacturer to ensure that its product is not misbranded and refused admission at the border, the finished product manufacturer should ensure that its API supplier is aware of the API manufacturer's obligation to register and ensure that the API manufacturer is actually registered and that the API is appropriately listed by the API manufacturer prior to importing the drug or offering the drug for import. Although the finished product manufacturer, in this scenario, is required to ensure that the API manufacturer is actually registered, it would not be proper for the finished product manufacturer, or anyone else who does not own or operate the API manufacturer, to submit an establishment registration on behalf of the API manufacturer, unless the finished product manufacturer or other person submitting the registration is an authorized agent of the API manufacturer.

VI. Severability

The purpose of this section is to clarify FDA's preliminary view with respect to the severability of provisions of this proposed rule. At this time, it is the Agency's position that the proposed provisions on foreign establishment registration and drug listing requirements are severable from the proposed revisions related to distributed manufacturing. Thus, if this rule

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[3] Additionally, the finished product manufacturer would need to identify the establishment where the API was manufactured as part of the drug listing for the finished product (see 21 CFR 207.49(a)(12)(ii)).

is finalized as proposed, and one or more of the DM provisions is determined by a court to be invalid, that partial invalidation should not render invalid any of the foreign establishment registration and drug listing provisions of the final rule. In addition, it is the Agency's position that each of the proposed foreign establishment registration and drug listing provisions in this proposed rule is generally capable of operating independently from the other proposed foreign establishment registration and drug listing provisions. Therefore, if the application of any portion of such provisions of this rule is determined to be invalid with respect to a particular circumstance, the Agency intends that such provisions would remain applicable to all other circumstances.

It is also the Agency's position that the proposed revisions to § 207.1 of the codified are not severable from any other proposed revision to the codified regarding distributed manufacturing. Thus, if this rule is finalized as proposed, and one or more of the proposed definitions is determined by a court to be invalid, the remaining DM provisions of the final rule should also be rendered invalid (e.g., the requirement in § 207.17 to register a DME). However, if this proposed rule is finalized as proposed, and the application of any portion of a definition in § 207.1 related to DM is determined to be invalid with respect to a particular circumstance, the Agency intends that such definition would remain applicable to all other circumstances.

Finally, it is the Agency's position that each of the proposed revisions related to DM in §§ 207.17-207.29 are generally capable of operating independently from one another. Thus, if this rule is finalized as proposed, and none of the DM definitions specified in the previous paragraph is invalidated, but any of the DM-related provisions in §§ 207.17 - 207.29 are determined by a court to be invalid, the remaining DM provisions §§ 207.17-207.29 should not be rendered invalid. For example, if this proposed rule is finalized as proposed, and if a court were to invalidate § 207.29(b)(4) regarding expedited updates prior to changing the location of a mobile DMU, the remaining DM provisions in part 207 would not be invalidated

as long as the DM-related definitions in § 207.1 are not invalidated. Additionally, if this proposed rule is finalized as proposed, and the application of any portion of a provision in §§ 207.17-207.29 is determined to be invalid with respect to a particular circumstance, the Agency intends that such provision would remain applicable to all other circumstances.

The foregoing reflects the Agency's preliminary determination regarding the severability of the provisions of this rule, and the Agency solicits feedback from stakeholders regarding the severability of the provisions of this rule. To the extent the Agency revises our determination regarding the severability of the provisions of this rule, either based on further internal evaluations or stakeholder feedback, the Agency will include such revised determination in the final rule.

VII. Proposed Effective Date

FDA proposes that any final rule based on this proposal become effective 30 calendar days after publication in the *Federal Register*. FDA solicits comment on this proposed date.

VIII. Preliminary Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 14192, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

Executive Orders 12866 and 13563 direct us to assess all benefits and costs of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits. The Office of Information and Regulatory Affairs (OIRA) has determined that this proposed rule is a significant regulatory action under section 3(f) of Executive Order 12866.

Executive Order 14192 requires that any new incremental costs associated with certain significant regulatory actions "shall, to the extent permitted by law, be offset by the

elimination of existing costs associated with at least 10 prior regulations." This proposed rule, if finalized as proposed, is not expected to be an Executive Order 14192 regulatory action because it does not impose any more than de minimis regulatory costs.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed rule, if finalized, would impose no costs on U.S. businesses beyond the time to read and understand some succinct revisions to an existing regulation, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (Section 202(a)) requires us to prepare a written statement, which includes estimates of anticipated impacts, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year." The current threshold after adjustment for inflation is $193 million, using the most current (2025) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

The proposed DME registration requirements would result in benefits for industry, the government, and patients. Benefits include increased visibility into the drug supply chain, as the co-registration of DME hub and spokes would enable FDA to correctly map out each DM configuration and understand the relationships between all components, supporting FDA's efforts to prevent and mitigate drug shortages and respond to unsafe products. Because of lack of data, we discuss these benefits qualitatively.

In creating streamlined procedures specifically for registration of DMEs, the proposed rule, if finalized, would revise certain sections of 21 CFR 207. We consider the labor hours to read these sections of 21 CFR 207 as a cost to drug manufacturers. The proposed rule would also impose costs on FDA to update structured product labeling (SPL) submission schema, tools, and

internal databases. Using a pre-statute baseline in accordance with Office of Management and Budget (OMB) guidance on regulatory impact analysis, we also estimate costs to unregistered foreign firms required by section 510 of the Food, Drug, and Cosmetic Act (FD&C Act), as amended by section 2511 of the PREVENT Pandemics Act, to register and list with FDA. We assume that 50% of foreign costs would be passed through to domestic entities. We additionally estimate some FDA labor costs to assist these foreign registrants.

We also identify cost savings to firms and the government. By consolidating individual DMU registrations, the proposed rule would reduce drug manufacturers' annual registration fees. FDA will also realize savings as less staff time will be required to review firm registration and answer technical and non-technical questions from registrants. Over ten years at a three percent discount rate, the estimated present value of the net costs of this proposed rule to domestic and foreign entities ranges from approximately $4.6 million to $5.78 million, with a primary estimate of $5.09 million. Estimated annualized net costs to domestic and foreign entities range from $0.48 million to $0.61 million at a three percent discount rate, with a primary estimate of $0.53 million. At a seven percent discount rate, the estimated present value of net costs ranges from $4.28 million to $5.33 million, with a primary estimate of $4.69 million. Estimated annualized net costs range from $0.53 million to $0.66 million at a seven percent discount rate, with a primary estimate of $0.58 million.

Table 1.--Summary of Benefits, Costs, and Distributional Effects of the Proposed Rule (2024 USD)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized				2024	7%	10 years	
					2024	3%	10 years	
	Annualized Quantified					7%		
						3%		
	Qualitative	More visibility into the drug supply chain would enhance FDA's ability to prevent unsafe products from reaching U.S. patients and support FDA's efforts with respect to preventing and mitigating drug shortages.						
Costs	Annualized Monetized	$583,958	$532,811	$664,495	2024	7%	10 years	At a seven percent discount rate, costs passed through by foreign entities are $582,675, and costs
		$533,771	$482,472	$606,839	2024	3%	10 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
								incurred by domestic entities are $1,283. We assume that 50% of foreign costs would be passed through to the U.S.
Transfers	Federal Annualized Monetized ($millions/ year)				2024	7%	10 years	
					2024	3%	10 years	
		From:			To:			
	Other Annualized Monetized ($millions/ year)				2024	7%	10 years	
					2024	3%	10 years	
		From:			To:			
	Effects	State, Local or Tribal Government: Small Business: Wages: Growth:						

We have developed a Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 9) and at https://www.fda.gov/about-fda/economics-staff/regulatory-impact-analyses-ria.

IX. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) that this action is of a type that does not normally have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

X. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). A description of these provisions is given in the *Description* section of this document with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering, and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Drug Establishment Registration and Drug Listing Requirements for Establishments Engaged in Distributed Manufacturing and Certain Foreign Establishments (0910-NEW)

Description: The proposed rule, if finalized, would revise the current registration regulations in part 207 to provide clear instructions specific to registering DMEs. 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 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 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 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. We use submission of 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 CGMP requirements or are otherwise adulterated or misbranded. These statutory provisions provide better visibility into foreign sources of drugs, including their components, which might enable more narrowly targeted responses to safety concerns related to certain known suppliers.

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.

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

Table 2.--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[2]
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
Total			52.355		103,819

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] 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), and the hour burden estimates applicable to these 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 this document. 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 this document. 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 2. 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 2.

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 for establishments 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 and 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 their establishments and list their drugs with FDA pursuant to section 510 of the FD&C Act, as amended by section 2511 of the PREVENT Pandemics Act, would more clearly understand their establishment registration and drug listing obligations. 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 establishment registration and drug 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 establishments 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 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 one 1.8 hours to submit an initial foreign establishment registration and 0.9 hour (54 minutes) to update a registration, as shown in Table 2.

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 2.

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 establishment registration and drug 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.

To ensure that comments on information collection are received, OMB recommends that written comments be submitted through reginfo.gov (see ADDRESSES). All comments should be identified with the title of the information collection.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3407(d)), we have submitted the information collection provisions of this proposed rule to OMB for review. These information collection requirements will not be effective until FDA publishes a final rule, OMB approves the information collection requirements, and the rule goes into effect. FDA will announce OMB approval of these requirements in the *Federal Register*.

XI. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

XII. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XIII. References

The following references are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at https://www.regulations.gov. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

1. CDER's Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) Initiative, available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cders-framework-regulatory-advanced-manufacturing-evaluation-frame-initiative
2. Safeguarding Pharmaceutical Supply Chains in a Global Economy: Hearing Before the House Committee on Energy and Commerce, Subcommittee on Health, 116st Cong. (2019) (Testimony of Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research at the Food and Drug Administration at the Department of Health and Human Services), available at https://www.fda.gov/news-events/congressional-testimony/safeguarding-pharmaceutical-supply-chains-global-economy-10302019.
3. Food and Drug Administration (FDA) Report on the State of Pharmaceutical Quality (FY2024), available at https://www.fda.gov/media/188153/download?attachment
4. FDA Distributed Manufacturing and Point-of-Care Manufacturing of Drugs Discussion Paper, available at https://www.federalregister.gov/documents/2022/10/14/2022-22386/discussion-paper-distributed-manufacturing-and-point-of-care-manufacturing-of-drugs-request-for.
5. FDA, Distributed Manufacturing of Drugs: Stakeholder Feedback and Action Plan, available at https://www.fda.gov/media/173449/download?attachment.
6. FDA, FDA/PQRI Workshop on the Regulatory Framework for Distributed and Point of Care Pharmaceutical Manufacturing, available at https://www.fda.gov/drugs/news-events-human-drugs/fdapqri-workshop-regulatory-framework-distributed-and-point-care-pharmaceutical-manufacturing#event-information.

7. FDA, Investigations Operations Manual, available at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/investigations-operations-manual.
8. FDA guidance for industry "Specification of the Unique Facility Identifier (UFI) System for Drug Establishment," November 6, 2014, available at https://www.fda.gov/media/89926/download.
9. FDA, Preliminary Regulatory Impact Analysis: Drug Establishment Registration Requirements for Establishments Engaged in Distributed Manufacturing and Certain Foreign Establishments, available at https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.

List of Subjects in 21 CFR Part 207

Drugs, Reporting and recordkeeping requirements.

For the reasons set forth in the preamble, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, the Food and Drug Administration proposes to amend 21 CFR part 207 as follows:

PART 207—REQUIREMENTS FOR FOREIGN AND DOMESTIC ESTABLISHMENT REGISTRATION AND LISTING FOR HUMAN DRUGS, INCLUDING DRUGS THAT ARE REGULATED UNDER A BIOLOGICS LICENSE APPLICATION, AND ANIMAL DRUGS, AND THE NATIONAL DRUG CODE

1. The authority citation for part 207 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360b, 371,374, 381, 393; 42 U.S.C. 262, 264, and 271.

§ 207.1 [Amended]

2. Amend § 207.1 as follows:

a. Add the definitions of "Distributed Manufacturing Establishment," Distributed Manufacturing Hub," and "Distributed Manufacturing Unit"; and

b. Revise the definitions of "Domestic," "Establishment," and "Foreign."

The addition and revisions read as follows:

Subpart A--General

§ 207.1 What definitions and interpretations of terms apply to this part?

* * * * *

Distributed manufacturing establishment means the distributed manufacturing hub together with one or more distributed manufacturing units (1) demonstrated to be and that remain equivalent in design and operation at any location, (2) that engage in the manufacture, preparation, propagation, compounding, or processing of the same drug(s) at one or more physical location(s), and (3) under the oversight and control of a single quality unit, which has a management structure located at the distributed manufacturing hub and has implemented a unified pharmaceutical quality system; provided that the distributed manufacturing hub and all distributed manufacturing units collectively (a) operate under one management pursuant to a manufacturing strategy designed to be decentralized; and (b) were subject to a preapproval inspection in connection with an approved marketing application that describes the use of a decentralized manufacturing strategy for at least one drug of each profile class manufactured by the distributed manufacturing establishment and was submitted under section 505(b)(1) and approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act; submitted and approved under section 505(j) of the Federal Food, Drug, and Cosmetic Act; submitted under section 512(b)(1) and approved under section 512(c)(1) of the Federal Food, Drug, and Cosmetic Act; submitted under section 512(b)(2) and approved under 512(c)(2) of the Federal Food, Drug, and Cosmetic Act; or submitted and approved under section 351(a) or (k) of the Public Health Service Act. A distributed manufacturing establishment must include either at least one distributed manufacturing unit capable of moving or being moved to another physical location or

at least two distributed manufacturing units if none of the distributed manufacturing units are capable of mobility.

Distributed manufacturing hub means the place of business at one general physical location that is the primary location of the quality unit responsible for implementing the unified pharmaceutical quality system to direct, monitor, and control the manufacture of drugs to ensure product quality at the distributed manufacturing establishment, including ensuring that all distributed manufacturing units within the distributed manufacturing establishment at any location are and remain equivalent in design and operation.

Distributed manufacturing unit means a physical unit engaged in the manufacture, preparation, propagation, compounding, or processing of a drug(s) that is generally deployed, or put into effect, at a separate location from the distributed manufacturing hub and that may further move from one general physical location to another if the unit is capable of mobility.

Domestic for purposes of registration and listing under this part:

(1) When used to modify the term "registrant," "manufacturer," "repacker," "relabeler," "salvager," "private label distributor," or "establishment" refers to a registrant, manufacturer, repacker, relabeler, salvager, private label distributor, or establishment within any State or Territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

(2) When used to modify the terms "distributed manufacturing hub" or "distributed manufacturing unit" refers to a distributed manufacturing hub or unit located within any State or Territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

* * *

Establishment, except when used in the term distributed manufacturing establishment, means a place of business under one management at one general physical location. Notwithstanding the foregoing, the term includes distributed manufacturing establishments. The term also includes, among others, independent laboratories that engage in control activities for a registered drug establishment (e.g., consulting laboratories), manufacturers of medicated feeds

and of vitamin products that are drugs in accordance with section 201(g) of the Federal Food, Drug, and Cosmetic Act, human blood donor centers, and animal facilities used for the production or control testing of licensed biologicals, and establishments engaged in salvaging.

* * *

Foreign for the purposes of registration and listing under this part:

(1) When used to modify the term "manufacturer," "repacker," "relabeler," or "salvager," refers to a manufacturer, repacker, relabeler, or salvager, who is located in a foreign country and who manufactures, repacks, relabels, or salvages a drug, or an animal feed bearing or containing a new animal drug, that is imported or offered for import into the United States.

(2) When used to modify the term "establishment" refers to an establishment that is located in a foreign country and is engaged in the manufacture, repackaging, relabeling, or salvaging of any drug, or any animal feed bearing or containing a new animal drug, that is imported or offered for import into the United States.

(3) When used to modify the term "distributed manufacturing hub" or "distributed manufacturing unit" refers to a distributed manufacturing hub or unit located in a foreign country, provided that the distributed manufacturing establishment for which the distributed manufacturing hub or unit is a part of is engaged in the manufacture of any drug, or any animal feed bearing or containing a new animal drug, that is imported or offered for import into the United States.

* * * * *

§ 207.17 [Amended]

3. Amend § 207.17 as follows:

a. Revise paragraph (a);

b. Redesignate paragraph (b) as paragraph (c); and

c. Add new paragraph (b).

The revisions and addition read as follows:

Subpart B--Registration

§ 207.17 Who must register?

(a) Unless exempt under section 510(g) of the Federal Food, Drug, and Cosmetic Act or this part, all manufacturers, repackers, relabelers, and salvagers must register each:

(1) Domestic establishment that manufactures, repacks, relabels, or salvages a drug, or an animal feed bearing or containing a new animal drug, and

(2) Foreign establishment that manufactures, repacks, relabels, or salvages a drug, or an animal feed bearing or containing a new animal drug, that is imported or offered for import into the United States regardless of whether the drug, or animal feed bearing or containing a new animal drug undergoes further manufacture, preparation, propagation, compounding, or processing at a separate foreign establishment prior to being imported or offered for import into the United States.

When operations are conducted at more than one establishment and common ownership and control among all the establishments exists, the parent, subsidiary, or affiliate company may submit registration information for all establishments.

(b) Unless exempt under section 510(g) of the Federal Food, Drug, and Cosmetic Act or this part, all manufacturers must register each distributed manufacturing establishment that includes (i) a domestic distributed manufacturing hub or unit, or (ii) a foreign distributed manufacturing hub or unit that manufactures a drug, or an animal feed bearing or containing a new animal drug that is imported or offered for import into the United States regardless of whether the drug, or animal feed bearing or containing a new animal drug undergoes further manufacture, preparation, propagation, compounding, or processing at a separate foreign establishment prior to being imported or offered for import into the United States.

(c) Private label distributors who do not also manufacture, repack, relabel, or salvage drugs are not required to register under this part. FDA will accept registration or listing information submitted by a private label distributor only if it is acting as an authorized agent for

and submitting information that pertains to an establishment that manufactures, repacks, relabels, or salvages drugs.

§ 207.21 [Amended]

4. Revise § 207.21 to read as follows:

§ 207.21 When must initial registration information be provided?

(a) For establishments other than distributed manufacturing establishments:

(1) Registrants must register each domestic establishment no later than 5 calendar days after beginning to manufacture, repack, relabel, or salvage a drug or an animal feed bearing or containing a new animal drug at such establishment.

(2) Registrants must register each foreign establishment before a drug or an animal feed bearing or containing a new animal drug manufactured, repacked, relabeled, or salvaged at the establishment is imported or offered for import into the United States.

(b) For distributed manufacturing establishments:

(1) Registrants must register each distributed manufacturing establishment no later than (i) 5 calendar days after the first domestic distributed manufacturing hub or unit begins to manufacture a drug or an animal feed bearing or containing a new drug for commercial distribution, or (ii) before a drug or an animal feed bearing or containing a new animal drug manufactured at any foreign distributed manufacturing hub or unit is imported or offered for import into the United States, whichever between (i) and (ii) occurs first.

(2) For a distributed manufacturing establishment in which the distributed manufacturing hub is located at, and operated as part of, a currently registered establishment, the registrant must update the existing establishment registration as described in § 207.29(b)(1) in lieu of a separate initial registration for the distributed manufacturing establishment.

§ 207.25 [Amended]

5. Amend § 207.25 as follows:

a. Revise paragraphs (a) and (b); and

b. Remove paragraphs (c)-(h).

The revisions read as follows:

§ 207.25 What information is required for registration?

* * *

(a) For establishments other than distributed manufacturing establishments:

(1) Name of the owner or operator of each establishment; if a partnership, the name of each partner; if a corporation, the name of each corporate officer and director, and the place of incorporation;

(2) Each establishment's name, physical address, and telephone number(s);

(3) All name(s) of the establishment, including names under which the establishment conducts business or names by which the establishment is known;

(4) Registration number of each establishment, if previously assigned by FDA;

(5) A Unique Facility Identifier in accordance with the system specified under section 510 of the Federal Food, Drug, and Cosmetic Act;

(6) All types of operations performed at each establishment;

(7) Name, mailing address, telephone number, and email address of the official contact for the establishment, as provided in § 207.69(a); and

(8) Additionally, with respect to foreign establishments subject to registration, the name, mailing address, telephone number, and email address must be provided for:

(i) The United States agent, as provided in § 207.69(b);

(ii) Each importer in the United States of drugs manufactured, repacked, relabeled, or salvaged at the establishment that is known to the establishment; and

(iii) Each person who imports or offers for import such drug to the United States.

(b) For distributed manufacturing establishments:

(1) Name of the owner or operator of each distributed manufacturing establishment; if a partnership, the name of each partner; if a corporation, the name of each corporate officer and director, and the place of incorporation;

(2) The name, physical address, and telephone number(s) of the distributed manufacturing hub of the distributed manufacturing establishment;

(3) All name(s) of the distributed manufacturing establishment, including names under which the distributed manufacturing establishment conducts business or names by which the distributed manufacturing establishment is known;

(4) Registration number of the distributed manufacturing establishment, if previously assigned by FDA;

(5) A Unique Facility Identifier of the distributed manufacturing establishment in accordance with the system specified under section 510 of the Federal Food, Drug, and Cosmetic Act;

(6) For each distributed manufacturing unit(s) of the distributed manufacturing establishment:

(i) The unit identifier for a distributed manufacturing unit, if previously assigned by FDA; and

(ii) The location of each distributed manufacturing unit, which may be a physical address or global positioning system (GPS) coordinates;

(7) All types of operations performed at each distributed manufacturing establishment, which include operations conducted at both the distributed manufacturing hub and the distributed manufacturing unit(s);

(8) Name, mailing address, telephone number, and email address of the official contact for the distributed manufacturing establishment, as provided in § 207.69(a);

(9) With respect to distributed manufacturing establishments including a foreign distributed manufacturing hub, the name, mailing address, telephone number, and email address must be provided for:

(i) The United States agent, as provided in § 207.69(b);

(ii) Each importer in the United States of drugs manufactured at a foreign distributed manufacturing unit or hub; and

(iii) Each person who imports or offers for import such drug to the United States.

(10) With respect to distributed manufacturing establishments including a domestic distributed manufacturing hub and at least one foreign distributed manufacturing unit, the name, mailing address, telephone number, and email address must be provided for:

(i) Each importer in the United States of drugs manufactured at a foreign distributed manufacturing unit or hub; and

(ii) Each person who imports or offers for import such drug to the United States.

§ 207.29 [Amended]

6. Amend § 207.29 as follows:

a. Revise the heading of paragraph (a);

b. Redesignate paragraph (b) as paragraph (c); and

c. Add new paragraph (b).

The revisions and addition read as follows:

§ 207.29 What are the requirements for reviewing and updating registration information?

(a) *Expedited updates for establishments other than distributed manufacturing establishments.* * * *

* * * * *

(b) *Expedited updates for distributed manufacturing establishments.*

(1) Registrants must update their registration when first registering a distributed manufacturing establishment in which the distributed manufacturing hub is located at, and

operated as part of, a currently registered establishment, following the timeline specified in § 207.21(b)(1). The expedited update must include the information required under § 207.25(b).

(2) Registrants must update their registration when adding a new distributed manufacturing unit to a previously registered distributed manufacturing establishment, no later than (i) 5 calendar days after a domestic distributed manufacturing unit begins to manufacture a drug or an animal feed bearing or containing a new drug for commercial distribution, or (ii) before a drug or an animal feed bearing or containing a new animal drug manufactured at a foreign distributed manufacturing unit is imported or offered for import into the United States. The expedited update must include the information required under § 207.25(b)(6).

(3) Registrants must update their registration information no later than 30 calendar days after:

(i) Removing a distributed manufacturing unit from a distributed manufacturing establishment. In addition to voluntary removal of a distributed manufacturing unit from a distributed manufacturing establishment, a registrant must remove a distributed manufacturing unit from a distributed manufacturing establishment when the registrant discontinues manufacturing at the distributed manufacturing unit or when the distributed manufacturing unit no longer remains equivalent in design and operations, and the registrant has not taken steps to return the DMU to being equivalent in design and operations;

(ii) Changing the name of a distributed manufacturing establishment;

(iii) Changing the physical address of the distributed manufacturing hub;

(iv) Closing or selling a distributed manufacturing establishment;

(v) Changing the name, mailing address, telephone number, or email address of the official contact or the United States agent. A registrant or United States agent may notify FDA about a change of information for the United States agent, but only a registrant is permitted to designate a new United States agent.

(4)(i) For a distributed manufacturing unit that is capable of moving or being moved to a new physical location, prior to changing the location of such distributed manufacturing unit the registrant must update their registration by providing advance notice as follows:

(1) For a location change within or to the United States, registrants must provide notice at least 30 calendar days prior to the relocation; or

(2) For a location change within or to a foreign country, registrants must provide notice at least 120 calendar days prior to the relocation.

(ii) The notification must include the unit identifier; the location from which the unit is departing (physical address or GPS coordinates); anticipated departure date; the destination location (physical address or GPS coordinates); anticipated arrival date; anticipated date to begin manufacturing operations at the new location.

(iii) The registrant must update the registration to confirm that the distributed manufacturing unit has arrived at the location specified in § 207.29(b)(4)(ii) and that manufacturing has commenced. The registrant must provide this update no later than 5 calendar days after a domestic distributed manufacturing unit begins to manufacture a drug or an animal feed bearing or containing a new drug for commercial distribution, or before a drug or an animal feed bearing or containing a new animal drug manufactured at a foreign distributed manufacturing unit is imported or offered for import into the United States.

(c) *Annual review and update of registration information.* Registrants must review and update all registration information required under § 207.25 for each establishment.

(1) The first review and update must occur during the period beginning on October 1 and ending December 31 of the year of initial registration, if the initial registration occurs prior to October 1. Subsequent reviews and updates must occur annually, during the period beginning on October 1 and ending December 31 of each calendar year.

(2) The updates must reflect all changes that have occurred since the last annual review and update.

(3) If no changes have occurred since the last registration, registrants must certify that no changes have occurred.

§ 207.41 [Amended]

7. In § 207.41, add new paragraph (d) to read as follows:

Subpart D--Listing

§ 207.41 Who must list drugs and what drugs must they list?

* * * * *

(d) Each registrant must comply with the requirements set forth in subsections (a), (b), and (c) of this section with respect to any drug that it manufactures, repacks, relabels, or salvages for commercial distribution at a foreign establishment regardless of whether such drug undergoes further manufacture, preparation, propagation, compounding, or processing at a separate foreign establishment prior to being imported or offered for import into the United States.

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Robert F. Kennedy, Jr.,

Secretary,

Department of Health and Human Services.

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