DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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

Docket No. FDA-2025-N-6075

Preliminary Regulatory Impact Analysis
Initial Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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Executive Summary

This proposed rule, if finalized, would revise drug manufacturing establishment registration regulations to provide instructions specifically for registering distributed manufacturing establishments. Distributed manufacturing is a decentralized manufacturing strategy that uses advanced manufacturing technology. For the purpose of this proposed rule, a distributed manufacturing establishment (DME) uses a "hub-and-spoke" model that consists of DM units (i.e., DMUs or the "spokes") that are equivalent in design and operation and manufacture the same drug(s) at multiple geographic locations under the oversight and control of a single quality unit that implements a unified pharmaceutical quality system (UPQS) with a management structure at the DM "hub." If finalized, this proposed rule would also update the drug establishment registration and listing requirements for foreign establishments to align the regulations with the recent changes made by Congress to section 510 of the FD&C Act.

We briefly describe the qualitative benefits to drug manufacturers and FDA from eliminating redundancy related to registering a network of DMUs. 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. 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 well as FDA labor costs to assist these foreign registrants; 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. 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, estimated annualized net costs range from approximately $482,472 to $606,839, with a primary estimate of $533,771.

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I. **Introduction and Summary**

A. Introduction

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.

B. Overview of Benefits, Costs, and Transfers

For the purpose of this proposed rule, 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.

If finalized, the proposed rule would revise the current registration regulations in 21 CFR 207 to provide clear instructions specifically for registering DMEs and eliminate redundancy in the registration process with regard to registering a network of DMUs.

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

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[1]. 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 (Ref. [1]), 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 additionally estimate some FDA labor costs to assist these foreign registrants. 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. These statutory provisions are self-implementing. We assume that 50% of foreign costs would be passed through to domestic entities.

We also identify cost savings to firms and the government. By consolidating individual DMU registrations, the proposed rule would reduce drug manufacturers' annual registration costs. 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 ranges from approximately $4.6 million to $5.78 million, with a primary estimate of $5.09 million. Estimated annualized net costs 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.

[1] 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, 21 C.F.R. pt. 207 (2016). https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-207

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 incurred by domestic entities are $1,283. We assume that 50% of foreign costs would be passed through to the U.S.
		$533,771	$482,472	$606,839	2024	3%	10 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Transfers	Federal Annualized Monetized ($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 request comment on our estimates of benefits, costs, and transfers of this proposed rule.

II. **Preliminary Economic Analysis of Impacts**

A. Background

FDA has observed a rapid emergence of advanced manufacturing technologies and recognized a need to update regulations to flexibly consider such new advancements. In 2014, FDA's Center for Drug Evaluation and Research (CDER) established the Emerging Technology Program (ETP) to facilitate meetings between industry representatives and FDA staff to discuss, identify, and resolve potential technical and regulatory issues regarding the development and

implementation of a novel technology prior to filing a regulatory submission.[2] In the first four years of the ETP, CDER received 46 requests to participate. In the past four years, 2022-2025, CDER received 109 such requests.

Since 2020, CDER has held ETP meetings related to distributed manufacturing (DM), a decentralized manufacturing strategy that uses advanced manufacturing technology. For the purpose of this proposed rule, a distributed manufacturing establishment (DME) follows a hub-and-spoke model that consists of "spokes" at multiple geographic locations where DM units (i.e., DMUs) that are equivalent in design and operation manufacture the same drug(s). The manufacturing activities at the DMUs are conducted under the oversight and control of a single quality unit that implements a unified pharmaceutical quality system (UPQS) with a management structure located at the DM "hub." DMUs can be added, removed, or relocated as needed to meet demand. For example, DMUs might be relocated as needed to address drug shortages related to supply chain challenges. Such deployment of DMUs might alleviate the impacts of public health emergencies on vulnerable populations.

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. However, 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. Although there may be other models of distributed manufacturing, it is likely that the burdens of applying the proposed streamlined registration pathway to such models would outweigh the benefits. Therefore, we have focused on the hub-and-spoke model.

However, current registration regulations generally consider manufacturing units located at different locations to be separate establishments and do not contemplate the mobility of manufacturing units. As such, current regulations would impose costly redundancy on manufacturers seeking to register multiple DMUs in a network and potential uncertainty if they were to relocate a DMU capable of mobility.

With respect to foreign establishment registration and drug listing requirements, 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 Federal Food, Drug, and Cosmetic Act (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 to 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.

[2] For additional information about the Emerging Technology Program, visit https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program-etp.

B. Need for Federal Regulatory Action

Under the existing regulations governing establishment registration, the term "establishment" is defined, in part, as "a place of business under one management at one general physical location" (21 CFR 207.1). Unlike a traditional drug manufacturing establishment, DMEs are designed to operate at more than one physical location. Under the current regulations, a DME consisting of a hub-and-spoke model as described above would be required to submit a separate registration for (1) each DMU that is manufacturing drugs at a different location; (2) the DM hub, provided it is engaged in manufacturing activities as defined in § 207.1; and (3) any DMU subsequently added at a new location. These separate registrations would not reveal to FDA the linked structure of a DME. In addition, registrants of DMEs might need to make multiple and frequent updates of the physical address as mobile units relocate. Current registration regulations do not contemplate mobile units distributed to various locations and registrants would not be required to notify FDA of the relocation of a DMU until 30 days after the change in physical address. In the case of a unit designed for mobility, this delay could create a problematic gap in FDA's oversight. With certain modifications to the type of information reported and the frequency of updates, a single registration could otherwise suffice for FDA's regulatory responsibilities.

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.

C. Purpose of the Proposed Rule

The proposed rule would revise the current registration regulations in 21 CFR 207 to provide clear instructions specific to registering DMEs. The proposed rule would eliminate redundancy by not treating DMUs within a DME as individual establishments requiring separate registrations.

The proposed rule would also update the registration and listing regulations applicable to foreign establishments to be consistent with recent clarifying changes to the statute made by section 2511 of the PREVENT Pandemics Act in order to eliminate any perceived inconsistencies between statutory requirements and the regulatory requirements in part 207.

D. Baseline Conditions

While no current regulatory submissions to CDER relate to DM, Emerging Technology Team (ETT) staff have met in the past year with seven companies developing technologies related to DM. As companies participating in the ETP have not yet filed, we cannot predict with certainty how many of these participants will ultimately submit filings related to DM or when exactly they might do so. However, according to ETT staff, four ETP participants currently claim plans to submit regulatory filings related to DM within a year. This analysis thus assumes that DM submissions will begin in low single figures in the next year or two before gradually increasing over time.

At baseline, at a minimum, each DMU within a DME would have to be separately registered under the existing regulations. The current registration regulations in 21 CFR 207 are also insufficient to appropriately address relocation of DMUs that are capable of mobility. Specifically, without the rule, registrants would not be required to update an establishment

registration with FDA in advance of relocating a DMU, but instead would have up to 30 days after a move to update units' physical addresses in FDA's databases. We assume that registrants would wait the full 30 days before reporting such move.

With respect to foreign establishment registration and drug listing requirements, 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 have thus not yet complied with section 510 of the Food, Drug, and Cosmetic Act (FD&C Act), recently amended by section 2511 of the PREVENT Pandemics Act. We use a pre-statute baseline in accordance with OMB guidance on regulatory impact analysis (Ref. [1]), hence including registration and listing costs to these establishments in our estimates.

Based on estimates by FDA's Office of Quality Surveillance (OQS), we estimate that about 25 foreign manufacturing establishments not currently registered with FDA might manufacture the active pharmaceutical ingredient (API) for a product subject to an approved application that is imported or offered for import into the United States. Based also on estimates by OQS, we estimate that about 1,600 foreign manufacturing establishments not currently registered with FDA might manufacture the API for an over-the-counter (OTC) monograph drug that is imported or offered for import into the United States. We estimate that 24,550 drug listings (550 for drugs subject to an approved application and 24,000 for OTC monograph drugs) are associated with these establishments.

Some registrants register more than one establishment. Thus, extrapolating from the ratio of registrants to establishments presented by Table 2 in the Regulatory Impact Analysis of the 2016 "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 (5,900 registrants to 7,300 establishments) (Ref. [2]), we estimate that the above establishments and drugs correspond to about 1,313 distinct firms (= (25 + 1,600) x (5,900 / 7,300)).

E. Benefits of the Proposed Rule

The proposed rule would provide clear instructions specifically with regard to registration of DMEs and eliminate costly redundant efforts by manufacturers who register such establishments. The proposed rule would allow a single registration to cover all DMUs in a DME. While we do not expect this to influence the choice between using a DME versus a conventional manufacturing establishment, which would likely depend on more significant strategic considerations, we expect the proposed rule to marginally improve convenience for baseline future DMEs. 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.

DME-specific registration regulations would also increase visibility into the drug supply chain. Registering the DME hub and spokes together in the same registration would enable FDA to correctly map each DME configuration and understand the relationships between the DMUs and hub. Without the proposed rule, FDA might not have a clear understanding of the manufacturing scheme of all DMEs. Additionally, requiring advance notification of DMU relocations, as

opposed to up to 30 days after the move, would close a potentially problematic—in the distributed manufacturing context—regulatory knowledge gap that would prevent FDA from being able to efficiently assess CGMP compliance, continued equivalency across DMU locations, and the effectiveness of the UPQS.

In accordance with OMB guidance on regulatory impact analysis (Ref. [1]), we use a pre-statute baseline to consider the foreign establishment registration and drug listing requirements implemented by section 510 of the FD&C Act as amended by the PREVENT Pandemics Act. These statutory provisions provide better visibility into foreign sources of drugs and ingredients, which might enable more narrowly targeted responses to safety concerns related to certain known suppliers. For example, a World Health Organization (WHO) safety advisory on certain active pharmaceutical ingredients (APIs) from certain suppliers might otherwise affect more imports than necessary if FDA cannot determine the source of ingredients in imported drugs.

We expect improved supply chain visibility to help support FDA's efforts with respect to preventing and mitigating drug shortages. For lack of data on relevant safety and efficiency outcomes, we are unable to quantitatively estimate these benefits.

F. Costs of the Proposed Rule

This proposed rule aims to establish more efficient registration procedures for DMEs by amending sections of 21 CFR 207. We expect the proposed rule, if implemented, to reduce DM registration costs, and thereby also decrease the labor hours required of FDA staff to process these registrations and respond to both technical and non-technical inquiries from manufacturers. However, companies would also incur labor costs to familiarize themselves with the revised sections of 21 CFR 207, and FDA would incur costs to update SPL submission schema, tools, and internal databases.

Some foreign establishments subject to statutory registration and listing requirements recently clarified by section 2511 of the PREVENT Pandemics ACT will incur costs to learn about registration and listing in addition to reading and understanding the current rule. Additionally, for first-time foreign registrants, the proposed rule would impose one-time costs to register establishments and list drugs, as well as recurring renewal costs. While our main analysis addresses costs to domestic entities, we estimate these costs to foreign entities in section II.K "International Effects." We assume a rate of 50% pass-through to domestic entities and thus include half of these foreign costs in Table 1, section II.H "Summary of Benefits, Costs, and Transfers," and the analysis of regulatory alternatives in section II.I.[3]

[3] We consider cost pass-through from international firms to fall between 0-100% with a midpoint of 50%, which is consistent with the broad scope of the literature on this topic. While there are many peer-reviewed papers that look at cost pass-through, the majority are not able to be extrapolated for general purposes because they tend to be specific to the structure of a single industry and type of cost. We rely on a report called "Cost pass-through: theory, measurement, and potential policy implications" by RBB Economics (2014) for broad conclusions on this literature (Ref. [9]). While this report is not peer reviewed it summarizes the peer reviewed literature. The report concludes "In summary, the available evidence reveals a wide range of pass-through rates or elasticities. Absolute industry-wide pass-through can be as low as 20% but can also reach well over 100%. Pass-through elasticities may fall close to zero but in some cases they come close to one. However, there is not enough empirical evidence to tie these variations in pass-through to specific market features, as predicted by the theory described in the preceding chapters. In sum, we are able to draw little by way of solid conclusions in this respect."

1. Cost Savings from Consolidation of Distributed Manufacturing Registrations and Subsequent Renewals

We are uncertain as to the likely prevalence of distributed manufacturing in the coming years and request comment on this topic. Based on ETP participation, we generally expect that DM submissions will begin in low single figures in the next year or two before gradually increasing over time. 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 the rule, three to five new DMEs in each of the next three years, and then eight to ten new DMEs per following year. Table 2 below shows the cumulative number of DMEs we assume will be registered in each year over the ten years following the effective date of the rule.

Table 2. Assumed cumulative number of registered DMEs.

	Primary	Low	High
Year 1	1	0	2
Year 2	2	0	4
Year 3	3	0	6
Year 4	7	3	11
Year 5	11	6	16
Year 6	15	9	21
Year 7	24	17	31
Year 8	33	25	41
Year 9	42	33	51
Year 10	51	41	61

We are also uncertain as to the likely scale of distributed manufacturing operations in the coming years and request comment on this topic as well. 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. We also consider a lower count of two and a higher count of eight DMUs per DME.

Table 3 below shows the registrations and renewals avoided by the proposed rule, given our range of assumptions about the prevalence and scale of distributed manufacturing, in each year over ten years from the effective date of the rule.

Table 3. Avoided registrations and renewals.

	Avoided registrations			Avoided renewals		
	Primary	Low	High	Primary	Low	High
Year 1	4	0	16	0	0	0
Year 2	4	0	16	4	0	16
Year 3	4	0	16	8	0	32
Year 4	16	6	40	12	0	48

Year 5	16	6	40	28	6	88
Year 6	16	6	40	44	12	128
Year 7	36	16	80	60	18	168
Year 8	36	16	80	96	34	248
Year 9	36	16	80	132	50	328
Year 10	36	16	80	168	66	408

We assume that most drug manufacturers register establishments with FDA via third-party services. Based on consulting the websites of some of these services, we estimated in 2023 that the price to register an establishment by this method was approximately $400, which we adjust to approximately $409.65 dollars (actual value includes fractional cents) to reflect the value of the dollar in 2024 using the GDP deflator (Ref. [3]). We estimated by this same method that the price to renew a registration, as required annually, was approximately $250, which we adjust to $256.03 dollars to account for inflation. We assume that these prices approximately reflect the labor cost that drug makers incur when making these submissions themselves.

Based on these prices and the above assumed numbers of registrations and renewals, Table 4 shows the expected registration and renewal costs to registrants that the proposed rule would avoid over ten years from the effective date of the rule. For example, we calculate the primary estimate of avoided registration costs to registrants in year 1 as follows: 4 avoided registrations (the primary estimate of avoided year 1 registrations in Table 3) x $409.65 (plus fractional cents) per registration = $1,638.59).

Table 4. Avoided registration and renewal costs to registrants (2024 USD)

	Avoided registration costs to registrants			Avoided renewal costs to registrants		
	Primary	Low	High	Primary	Low	High
Year 1	$1,638.59	$0.00	$6,554.37	$0.00	$0.00	$0.00
Year 2	$1,638.59	$0.00	$6,554.37	$1,024.12	$0.00	$4,096.48
Year 3	$1,638.59	$0.00	$6,554.37	$2,048.24	$0.00	$8,192.96
Year 4	$6,554.37	$2,457.89	$16,385.92	$3,072.36	$0.00	$12,289.44
Year 5	$6,554.37	$2,457.89	$16,385.92	$7,168.84	$1,536.18	$22,530.63
Year 6	$6,554.37	$2,457.89	$16,385.92	$11,265.32	$3,072.36	$32,771.83
Year 7	$14,747.32	$6,554.37	$32,771.83	$15,361.80	$4,608.54	$43,013.03
Year 8	$14,747.32	$6,554.37	$32,771.83	$24,578.87	$8,705.02	$63,495.42
Year 9	$14,747.32	$6,554.37	$32,771.83	$33,795.95	$12,801.50	$83,977.82
Year 10	$14,747.32	$6,554.37	$32,771.83	$43,013.03	$16,897.98	$104,460.21

By reducing the number of registrations and renewals, the proposed rule would also reduce the time that FDA staff spends answering questions from SPL submitters attempting to troubleshoot technical issues. Based on an average of approximately 116,000 yearly SPL submissions between 2018-2022 (with no apparent upward or downward trend) and 3,500 technical questions related to SPLs per year, we estimate that submitters ask FDA staff about 0.03 technical questions per SPL submission (or roughly once in thirty-three submissions). We assume that questions not concerning technical issues, of which there are roughly another 3,500 per year,

would not necessarily scale with the number of SPL submissions. Hence, we do not consider that the proposed rule would reduce the labor spent answering non-technical questions.

For the purpose of determining time spent per question from total labor hours and total questions, we treat technical and non-technical questions as equally time-consuming. We estimate that FDA staff spend a total of 2,500 to 7,500 hours per year answering SPL-related questions, with a primary estimate of 5,000 hours. With about 7,000 total yearly questions (including the 3,500 that concern technical issues and the 3,500 that do not), we estimate that staff time spent per question ranges from about 0.35 to 1.07 hours on average, with a primary estimate of 0.71 hours (5,000 hours / 7,000 questions = 0.71 hours per question).

Based on the previous assumption that technical questions scale with SPL submissions at a rate of approximately 0.03 technical questions per SPL submission, each avoided SPL submission in turn avoids approximately 0.022 hours of FDA staff labor in the form of answering questions (0.03 questions per submission x 0.71 hours per question = 0.02 hours per submission). (Using the range of hours above (2,500 to 7,500) results in a range from approximately 0.011 to 0.032 hours.)

The hourly labor cost of an average employee in FDA's Center for Drug Evaluation and Research (CDER) in 2024 was $169.38, including benefits and overhead.

Table 5 below multiplies the avoided registrations and renewals from Table 3 above by our estimated range of FDA labor hours per SPL submission and by the labor cost of a CDER employee. For example, we calculate the primary estimate of avoided FDA labor costs related to registrations in year 1 as follows: 4 avoided registrations (the primary estimate of avoided year 1 registrations in Table 3) x 0.022 (approximate, rounded to thousandths) hours spent answering questions per registration x $169.38 per hour = $14.58. This calculation yields our estimates of the proposed rule's benefit to FDA over ten years in the form of avoided labor spent answering questions related to technical issues on SPL submissions.

Table 5. Avoided FDA labor costs related to answering questions on SPL submissions (2024 USD)

	Avoided FDA costs from registrations			Avoided FDA costs from renewals		
	Primary	Low	High	Primary	Low	High
Year 1	$14.58	$0.00	$87.49	$0.00	$0.00	$0.00
Year 2	$14.58	$0.00	$87.49	$14.58	$0.00	$87.49
Year 3	$14.58	$0.00	$87.49	$29.16	$0.00	$174.98
Year 4	$58.33	$10.94	$218.73	$43.75	$0.00	$262.47
Year 5	$58.33	$10.94	$218.73	$102.07	$10.94	$481.20
Year 6	$58.33	$10.94	$218.73	$160.40	$21.87	$699.93
Year 7	$131.24	$29.16	$437.46	$218.73	$32.81	$918.66
Year 8	$131.24	$29.16	$437.46	$349.97	$61.97	$1,356.12
Year 9	$131.24	$29.16	$437.46	$481.20	$91.14	$1,793.58
Year 10	$131.24	$29.16	$437.46	$612.44	$120.30	$2,231.04

2. Cost of Reading and Understanding

We assume that firms seeking to register a DME will incur a one-time cost to read and understand the rule in year one, the first year starting from the effective date of the rule. As the proposed rule intersperses the new regulatory language into existing sections of the Code of Federal Regulations (CFR) that govern non-DM drug establishment registration and listing, some firms who do not intend to register DMEs might also incur the cost of reading the DM-specific text. To account both for firms intending to register DMEs as well as those who might read the distributed manufacturing registration regulations incidentally—without intending to register DMEs specifically—we approximately double the year 10 counts of cumulative DME registrations from Table 2 (rounded to the nearest tens).

We assume that drug manufacturers will bear the cost of reading and understanding the rule, but there might be cases where this cost falls instead on third party registration services. To the extent that drug manufacturers rely on third party services for registration and listing—and that a single such third party can serve multiple manufacturers—we possibly overestimate the number of entities that would read the additional text. It is also possible that FDA's electronic forms obviate the need for either drug makers or registration services to read the regulation itself. In that case, we might overestimate the labor to understand how to submit and update DME registrations.

We estimate that the new parts of 21 CFR 207 related to distributed manufacturing contain approximately 2,000 words. Based on departmental guidelines for RIAs (Ref. [4]), we assume a reading speed of 225 words per minute, with a slower estimate of 200 and a faster estimate of 250. We therefore assume that the average employee of a drug maker would take about 0.15 hours to read the proposed revisions ((2,000 words / 225 words per minute) / 60 minutes per hour = 0.15 hours).

We assume that the employees who would read the revisions are lawyers. According to the Occupational Employment and Wage Statistics from the Bureau of Labor Statistics, the average hourly wage of a lawyer in NAICS 3254 Pharmaceutical and Medicine Manufacturing was $129.51 in 2024.[4] We obtain an hourly labor cost estimate of $259.02 by doubling $129.51 to account for benefits and overhead costs. We assume that the typical firm would have one employee read the revisions, but also consider a scenario with a higher estimate of two. Table 6 below shows our estimates of the one-time cost to read and understand the proposed revisions given our range of assumptions about reading speed and number of employees involved.

Table 6. One-time cost of reading and understanding the proposed revisions (2024 USD)

	Primary	Low	High
(a) Average reading speed (words/minute)	225	250	200
(b) Words in 21 CFR pt. 207	2,000	2,000	2,000
(c) Number of employees to read rule	1	1	2
(d) Labor cost of hourly employee	$259.02	$259.02	$259.02
(e) Hours to read and understand proposed rule = ((b/a)/60)	0.15	0.13	0.17
(f) Per firm cost = c * d * e	$38.37	$34.54	$86.34

[4] Bureau of Labor Statistics. May 2023 National Industry-Specific Occupational Employment and Wage Estimates NAICS 325400 - Pharmaceutical and Medicine Manufacturing. Available from: https://www.bls.gov/oes/current/naics4_325400.htm#23-0000

(g) Firms	100	80	120
(h) Total cost = g * f	$3,837	$2,763	$10,361

3. FDA Costs to Update SPL Submission Schema, Tools, and Internal Databases

The proposed revisions would cause FDA to incur one-time costs to update the SPL submission schema, tools, and internal databases. Currently, we lack details necessary to provide precise price estimates for these updates, but account for them with a primary estimate of $100,000, a low estimate of $50,000, and a high estimate of $200,000. While we are not yet able to provide a detailed list of necessary updates and their anticipated costs, FDA staff familiar with SPL systems considered this range at this time to encompass the reasonable possibilities. We assume that these would be upfront costs incurred upon publication of the proposed rule, early in year one, and hence they are undiscounted in the annualized costs shown in Table 1.

It is possible that drug manufacturers and any third-party registration services they use to register with FDA would also incur costs to modify SPL submission tools. We request public comment on the extent and cost of any modifications likely to be needed.

4. FDA Labor Costs to Assist Foreign Establishment Registrants

Clarifying changes to statute made by section 2511 of the PREVENT Pandemics Act might increase compliance among certain foreign establishments with registration and listing requirements. We expect that FDA might incur some labor costs to assist with new foreign registrants. These statutory provisions are self-implementing even in the absence of the current regulatory action. In accordance with OMB guidance on regulatory impact analysis (Ref. [1]), we use a pre-statute baseline, thus including these costs in our analysis. We address costs potentially incurred by foreign establishments in section II.K "International Effects." While we are unsure of how much assistance these registrants will require from FDA, we use our estimates of FDA staff time for registrations and renewals from section II.F.1 "Cost Savings from Consolidation […]" to account approximately for these costs. Thus, we estimate an average of approximately 0.022 (rounded) FDA staff hours per registration (and subsequent yearly renewal), with a range from 0.011 to 0.032, at an hourly labor cost of $169.38. With our estimate of about 1,625 potentially affected foreign establishments, which we derive in section II.D "Baseline Conditions," we estimate an annual recurring cost of about $5,924 (= 0.022 hours (rounded) x $169.38 x 1,625 establishments), ranging from $2,962 to $8,886.

G. Transfers Caused by the Proposed Rule

As the Generic Drug User Fee Amendments (GDUFA) include an establishment fee, insufficient user fees might be collected from generic drug manufacturers when multiple DMUs compose a DME under a single registration. FDA might need to consider a different approach to establishment user fees for generic drug manufacturers, where applicable, based on the amount of FDA labor needed for a DME. For example, an establishment comprising twenty units might incur additional resource burden than one comprising ten units. However, pending future user fee negotiations, we lack information to quantitatively analyze the impact that the proposed rule would have on transfers.

Any impact on the net value of transfers per DMU—which under the current regulations would have to be registered individually—might depend on whether FDA will need to inspect all units in a DME.

If FDA will need to inspect all units in a DME, then the amount collected in user fees per DMU would likely need to approximately equal what would be collected under the current regulations. We note in this case that, with little or no reduction in user fees from consolidation of registrations, deploying a DME with many DMUs could be particularly challenging for manufacturers of certain generic drugs with low profit margins. However, if FDA will not need to inspect all units in a DME, then it might be possible for the amount collected in user fees per unit to decrease. This latter scenario might occur if FDA determines that DMEs can fall under more streamlined oversight due to all the units within an establishment being equivalent in design and operation.

H. Summary of Benefits, Costs, and Transfers

Unquantified benefits include enhanced oversight of the drug supply chain, leading to an increased capacity for the FDA to tackle patient safety issues and drug shortages. By registering the DME hub and spokes under a single registration, FDA would be able to map each DM configuration and better understand the connections between components. Furthermore, mandating advance notification of DMU relocations, rather than allowing notifications up to 30 days post-move, would bridge a potentially significant regulatory knowledge gap—in the context of distributed manufacturing—that could hinder FDA's ability to effectively evaluate CGMP compliance, maintain equivalency across DMU locations, and assess the efficacy of the UPQS.

Table 7 below summarizes estimated costs gross of savings. These costs are calculated and discounted over a ten-year period from the date of publication, which we currently expect to occur at the start of 2027.

The proposed rule would cause FDA to pay one-time costs to update SPL submission schema, tools, and internal databases. The proposed rule would also impose one-time costs on drug makers in the form of labor spent reading and understanding the distributed manufacturing registration regulations. Note that both savings from registration consolidation and year 1 costs (2027) of reading and understanding the rule depend on a shared assumption regarding the number of affected firms. As a result, each of the low, primary, and high overall net cost scenarios associates a particular reading cost estimate and savings estimate. The overall low net cost scenario results from the assumptions that produce the high reading cost and savings estimates, as savings outweigh reading costs.

Using a pre-statute baseline in accordance with OMB guidance on regulatory impact analysis (Ref. [1]), we also estimate costs to unregistered foreign firms who might comply with section 510 of the FD&C Act to register and list with FDA following clarifying changes to statute made by section 2511 of the PREVENT Pandemics Act. We estimate these costs in section II.K "International Effects." As we noted above, we assume that 50% of these foreign costs will be passed through to domestic entities and include half of these costs in this summary section, the analysis of regulatory alternatives in section II.I, and section I "Introduction and Summary."

Table 7. Summary of estimated gross costs of the rule over 10 years (2024 USD)

	Domestic			Pass-Through From Foreign Firms		
	Primary	Low	High	Primary	Low	High
Upon publication*	$100,000	$50,000	$200,000	$0	$0	$0
Year 1	$9,761	$13,323	$2,763	$3,647,073	$3,510,273	$4,125,120
Year 2	$5,924	$2,962	$8,886	$208,024	$208,024	$208,024
Year 3	$5,924	$2,962	$8,886	$208,024	$208,024	$208,024
Year 4	$5,924	$2,962	$8,886	$208,024	$208,024	$208,024
Year 5	$5,924	$2,962	$8,886	$208,024	$208,024	$208,024
Year 6	$5,924	$2,962	$8,886	$208,024	$208,024	$208,024
Year 7	$5,924	$2,962	$8,886	$208,024	$208,024	$208,024
Year 8	$5,924	$2,962	$8,886	$208,024	$208,024	$208,024
Year 9	$5,924	$2,962	$8,886	$208,024	$208,024	$208,024
Year 10	$5,924	$2,962	$8,886	$208,024	$208,024	$208,024
Total	$163,076	$89,980	$282,736	$5,519,292	$5,382,492	$5,997,339
Present Value (7%)	$145,193	$80,487	$256,688	$4,675,140	$4,547,290	$5,121,913
Present Value (3%)	$154,258	$85,325	$269,854	$5,113,372	$4,980,557	$5,577,495
Annualized Value (7%)	$18,096	$10,031	$31,992	$582,675	$566,741	$638,357
Annualized Value (3%)	$16,186	$8,953	$28,316	$536,544	$522,608	$585,244

*These are the upfront costs incurred by FDA to update SPL systems in order to be able to receive and process DME submissions. They occur at the start of year 1 and are thus undiscounted.

The proposed rule, if finalized, would also lead to cost savings from consolidation of DME registrations and renewals. Table 8 below summarizes the savings previously estimated in Table 4 and Table 5.

Table 8. Summary of estimated cost savings of the rule over 10 years (2024 USD)

	Primary	Low	High
Upon publication*	$0	$0	$0
Year 1	$1,653	$0	$6,642
Year 2	$2,692	$0	$10,826
Year 3	$3,731	$0	$15,010
Year 4	$9,729	$2,469	$29,157
Year 5	$13,884	$4,016	$39,616
Year 6	$18,038	$5,563	$50,076
Year 7	$30,459	$11,225	$77,141
Year 8	$39,807	$15,351	$98,061
Year 9	$49,156	$19,476	$118,981
Year 10	$58,504	$23,602	$139,901
Total	$227,653	$81,701	$585,410

Present Value (7%)	$134,897	$46,970	$352,721
Present Value (3%)	$180,680	$64,050	$467,827
Annualized Value (7%)	$16,813	$5,854	$43,961
Annualized Value (3%)	$18,959	$6,721	$49,089

*Note that the "high" savings scenario will correspond to the "low" net cost scenario and vice versa.

Overall, we anticipate net costs from this proposed rule. Table 9 below nets out cost savings from costs. Note that the "high" net cost scenario subtracts out the "low" cost savings from the "high" gross cost scenario.

Table 9. Summary of estimated net costs of the rule over 10 years (2024 USD)

	Domestic			Pass-Through From Foreign Firms		
	Primary	Low	High	Primary	Low	High
Upon publication*	$100,000	$50,000	$200,000	$0	$0	$0
Year 1	$8,108	$6,681	$2,763	$3,647,073	$3,510,273	$4,125,120
Year 2	$3,232	-$7,864	$8,886	$208,024	$208,024	$208,024
Year 3	$2,193	-$12,048	$8,886	$208,024	$208,024	$208,024
Year 4	-$3,805	-$26,195	$6,417	$208,024	$208,024	$208,024
Year 5	-$7,960	-$36,655	$4,870	$208,024	$208,024	$208,024
Year 6	-$12,115	-$47,114	$3,323	$208,024	$208,024	$208,024
Year 7	-$24,535	-$74,179	-$2,339	$208,024	$208,024	$208,024
Year 8	-$33,883	-$95,099	-$6,465	$208,024	$208,024	$208,024
Year 9	-$43,232	-$116,019	-$10,590	$208,024	$208,024	$208,024
Year 10	-$52,580	-$136,939	-$14,716	$208,024	$208,024	$208,024
Total	-$64,576	-$495,430	$201,034	$5,519,292	$5,382,492	$5,997,339
Present Value (7%)	$10,297	-$272,234	$209,718	$4,675,140	$4,547,290	$5,121,913
Present Value (3%)	-$26,422	-$382,501	$205,803	$5,113,372	$4,980,557	$5,577,495
Annualized Value (7%)	$1,283	-$33,929	$26,138	$582,675	$566,741	$638,357
Annualized Value (3%)	-$2,772	-$40,136	$21,595	$536,544	$522,608	$585,244

*These are the upfront costs incurred by FDA to update SPL systems in order to be able to receive and process DME submissions. They occur at the start of year 1 and are thus undiscounted.

I. Analysis of Regulatory Alternatives to the Proposed Rule

We analyze the following regulatory alternatives to the proposed rule:

1. With respect to distributed manufacturing, only revise registration regulations to update the timeline for notifying FDA of establishment relocations (to require advance notice instead of allowing up to 30 days post-move).

2. With respect to distributed manufacturing, only revise registration regulations to allow for the DMU itself to be the "one physical location" specified in 21 CFR 207.1.

1. Update only the timeline for notifying FDA of establishment relocation.

Unlike the proposed rule, this alternative would not reduce labor spent on initial registrations and yearly renewals compared to baseline. Additionally, under this alternative, FDA would not have visibility into the links between DMUs in a DME.

As under the proposed rule, which requires advance notice of the new physical address when relocating DMUs, FDA would have real-time knowledge of the physical addresses of DMUs.

This alternative would likely not require significant changes to FDA's SPL submissions schema, tools, and internal databases outside of what can be modified within the scope of baseline service. However, net costs of this alternative would exceed those of the proposed rule due to foregoing the cost savings that would otherwise result from consolidating registrations and renewals.

2. Allow for the DMU itself to be the "one general physical location" specified in 21 CFR 207.1

Compared to the proposed rule, this alternative might save registrants a small amount of labor when relocating DMUs by not requiring them to update a physical address in FDA's data. Due to uncertainty about how many DMUs would be designed for mobility and how often they would move, and also due to the small labor savings involved in notifying FDA of the new address, we do not attempt to quantify this benefit.

However, FDA would then not know the physical locations of DMUs, or the links between DMUs in a DME, which might create a problematic knowledge gap with respect to its regulatory responsibilities. Additionally, unlike the proposed rule, this alternative would not reduce labor spent on initial registrations and yearly renewals compared to baseline.

This alternative would likely not require significant changes to FDA's SPL submissions schema, tools, and internal databases outside of what can be modified within the scope of baseline service. However, net costs of this alternative would exceed those of the proposed rule due to foregoing the cost savings that would otherwise result from consolidating registrations and renewals.

Table 10 summarizes the primary estimates of costs and savings of the alternatives compared to those of the proposed rule. We annualize costs and savings over ten years.

Table 10. Annualized costs, savings, and net costs of the proposed rule and alternatives (2024 USD)

	Annualized costs (7%)	Annualized savings (7%)	Annualized net costs (7%)	Change in net costs from proposed rule (7%)
Alternative 1: Require advance notification of establishment relocation	$588,307	$0	$588,307	$4,349

Alternative 2: Allow the DMU to be the "one general physical location"	$588,307	$0	$588,307	$4,349
Proposed Rule	$600,771	$16,813	$583,958	N/A

J. Distributional Effects

We do not anticipate that the proposed rule will have any differential effects across the population and economy.

K. International Effects

Section 2511 of the PREVENT Pandemics Act amended section 510 of the Federal Food, Drug, and Cosmetic Act (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 to list such drugs.

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. These statutory provisions are self-implementing even in the absence of the current regulatory action. In accordance with OMB guidance on regulatory impact analysis (Ref. [1]), we use a pre-statute baseline, thus estimating the costs of these requirements.

In order to comply with these statutory requirements, some unregistered foreign firms need to learn about registration and listing, prepare standard operating procedures (SOPs), register establishments, list drugs, and renew registrations on a yearly basis.

1. Foreign Wages and Labor Time Adjustments

We do not know in which countries affected foreign firms are located because these firms are unregistered and do not import drugs directly into the U.S. However, we estimate foreign wages in this section by adjusting U.S. wages based on a comparison of U.S. and world gross domestic product (GDP) per capita. Additionally, we adjust estimates of foreign labor hours to account for different levels of English proficiency.

According to World Bank data from 2024, the U.S. GDP per capita of $84,534.0 is comparable to world GDP per capita of $13,631.2 expressed in U.S. dollars using exchange rates (Ref. [5]). We thus multiply the U.S. labor costs from section II.F by a factor of 0.16 (= 13,631.2 / 84,534.0), obtaining hourly labor costs of $28.79 and $41.77 for foreign managers and lawyers, respectively.

To account for differences in English proficiency, we multiply the hours estimated for compliance tasks by a factor of 1.8, the English proficiency adjustment used in the Regulatory Impact Analysis for the Tobacco Product Manufacturing Practice proposed rule (Ref. [6]). Hence, we estimate about 1.8 foreign labor hours for each hour spent by a US-based worker on tasks involving English proficiency.

2. Learning About FDA Registration and Listing

The Regulatory Impact Analysis of the 2016 "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 estimated that reading and understanding that rule would take 21 total hours per firm among all relevant employees. Since that 2016 rule codified the statutory requirements of the 2007 Food and Drug Administration Amendments Act (FDAAA) and the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) with respect to drug registration and listing, we use the previous 21 hour estimate as an approximation of the labor time necessary for a first-time registrant to learn how to register establishments and list drugs with FDA. Multiplying by 1.8 to account for English proficiency, we obtain an adjusted estimate of 37.8 hours.

We add to this the total hours of reading per firm for this current rule, estimated initially in section II.F.2 above, "Cost of Reading and Understanding," and scaled by a factor of 1.8 to account for English proficiency: 0.27 hours in the primary case (= 1 employee x 0.15 hours each x 1.8), 0.24 hours in the low case (= 1 employee x 0.13 hours x 1.8), and 0.60 hours in the high case (= 2 employees x 0.17 hours each x 1.8). Table 11 below shows our estimates of the costs to foreign firms to learn about registration and listing with FDA.

Using the $41.77 hourly labor cost of a lawyer in a foreign firm as estimated above we estimate a one-time cost per firm of about $1,590 (= (37.8 hours + 0.27 hours) x $41.77). Based on the 1,313 distinct first-time foreign registrants estimated in section II.D "Baseline Conditions," we estimate a one-time cost of about $2.09 million (= $1,590 x 1,313) for learning about registration and listing. We expect this cost to occur in year one, the first year starting from the effective date of the rule.

Table 11. One-time cost to learn about FDA registration and listing (2024 USD)

	Primary	Low	High
(a) Hours for general registration and listing	37.8	37.8	37.8
(b) Hours for proposed rule	0.27	0.24	0.60
(c) Hourly labor cost	$41.77	$41.77	$41.77
(d) Per firm cost = (a + b) * c	$1,589.94	$1,588.83	$1,603.86
(e) Firms	1,313	1,313	1,313
(f) Total cost = d * e	$2,087,592	$2,086,129	$2,105,872

3. Standard Operating Procedures (SOPs)

First-time foreign registrants will also incur a one-time cost in year one to write SOPs or adapt existing ones for registration and listing with FDA. Based on a report by Eastern Research Group (Ref. [7]), we estimate that the time for pharmaceutical manufacturers to prepare SOPs for

registration and listing with FDA ranges from 16 to 24 total labor hours, with a primary estimate of 20 hours. Multiplying by 1.8 to account for English proficiency, we obtain adjusted primary, low, and high estimates of 36.0, 28.8, and 43.2 hours. Table 12 below shows our estimates of the costs to foreign firms to write or adapt registration and listing SOPs.

We assume that the employees who would prepare the SOPs are at the managerial level and use the $28.79 hourly labor cost of a manager in a foreign firm as estimated above.

We thus estimate a cost per firm of about $1,036 (= 36 hours x $28.79), with a low estimate of about $829 and a high estimate of about $1,244.

Based on the 1,313 distinct first-time foreign registrants estimated in section II.D "Baseline Conditions," we estimate a one-time cost of about $1.36 million (= 1,313 x $1,036.32), with a low estimate of about $1.01 million and a high estimate of about $1.63 million.

Table 12. One-time cost for SOPs for registration and listing with FDA (2024 USD)

	Primary	Low	High
(a) Hours per firm	36.0	28.8	43.2
(b) Hourly labor cost	$28.79	$28.79	$28.79
(c) Per firm cost = a * b	$1,036.32	$829.05	$1,243.58
(d) Firms	1,313	1,313	1,313
(e) Total cost = c * d	$1,360,682	$1,088,546	$1,632,819

4. Initial Establishment Registration

Each unregistered foreign establishment that needs to register will incur a one-time cost of initial registration in year one. Based on the fee for third-party registration services estimated in section II.F.1, each first-time establishment registration would generate about $409.65 in costs.

Based on the 1,625 unregistered foreign establishments estimated in section II.D "Baseline Conditions" that would need to register, we estimate a one-time cost of about $665,678 (= $409.65 x 1,625).

5. Drug Listing

Foreign establishments required to list drugs will also incur one-time costs to do so in year one. According to FDA in 2016, drug listing requirements newly implemented at the time would add half an hour to the two hours previously needed for listing a drug (Ref. [2]). Thus, we estimate that listing a single drug requires 2.5 hours of labor, which we adjust to about 4.5 based on the foreign labor time adjustment calculated in section II.K.1 (= 2.5 *1.8). Using the $28.79 hourly management labor cost estimated above yields a cost of $129.54 per drug listing (= $28.79 x 4.5 hours, with rounding).

Based on the 24,550 foreign drugs estimated in section II.D "Baseline Conditions" to require listing, we estimate a one-time cost of about $3,180,194 (= $129.54 x 24,550, with rounding).

6. Establishment Registration Renewal

Starting in year two, each foreign establishment required to register will incur a yearly recurring cost to renew its registration. Based on the fee for third-party registration renewal services estimated in section II.F.1, each renewal would generate about $256.03 in costs.

Based on the 1,625 foreign establishments estimated in section II.D "Baseline Conditions" to need to register, we estimate a recurring cost of about $416,049 (= $256.03 x 1,625).

L. Uncertainty and Sensitivity Analysis

As stated in section II.F.1 "Cost Savings from Consolidation […]," we are uncertain as to the likely prevalence of distributed manufacturing in the coming years and request comment on this topic.

The costs related to DME registration—updates to FDA's SPL submission schema, tools, and internal databases, and industry labor for reading and understanding the needed revisions to 21 CFR 207—are fixed and do not change with the number of DMUs in applications relevant to the proposed rule.

Lacking quantitative information with which to project future distributed manufacturing, section II.F.1 shows what we consider to be possible scenarios. However, the specific range of scenarios chosen is illustrative and not necessary to demonstrate any analytical implications. In all scenarios shown, we scale an approximately known cost savings—i.e., avoided third-party service fees for registration (or equivalently the labor to register one's own establishments)—linearly with the difference between the number of DMUs overseen by hubs.

All parameters scale the final estimated costs and benefits linearly. Thus, readers can apply this method to any scenario of interest, in terms of future distributed manufacturing, by multiplying their preferred parameter estimates per section II.F.

We do not account for nonlinearities, which we do not know about but might exist or come to exist in the future. For example, the ability to have a single registration cover a DME with several DMUs might prompt manufacturers that formerly used third-party services to familiarize themselves with the registration process, whereupon these manufacturers might become more proficient at registering and thus use less labor than we have estimated. It is also possible that third-party services offer or would offer in the future discounts when registering a DME with several units. In such a case, we would likely have overestimated benefits.

With respect to foreign establishment registration and drug listing requirements, the numbers of firms and establishments that might not be currently registered with FDA because the drug they manufacture is only indirectly imported or offered for import into the United States—after undergoing further manufacture at another foreign establishment—are unknown. While for drugs subject to an approved application OQS was able to identify establishments submitted by application holders that did not subsequently register in eDRLS but would be required to do so if the proposed rule is finalized, it was not possible to do so for OTC monograph drugs. Namely, it is not possible to know how many distinct establishments manufacture the OTC monograph drugs listed without API facilities. Based on the number of establishments among OTC monograph drugs listed with API facilities, OQS extrapolated the number of establishments among those listed without API facilities.

While we adjust labor costs in section II.K "International Effects" based on comparing U.S. to world GDP per capita, we do not know where exactly most unregistered manufacturers of API imported into the U.S. are located. In general, we expect that most of these firms operate in places with lower costs of labor than the U.S.

III. **Initial Small Entity Analysis**

The Regulatory Flexibility Act (RFA) requires Agencies 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, if finalized, will not have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document and the preamble of the proposed rule, serves as the Initial Regulatory Flexibility Analysis, as required under the RFA.

A. Description and Number of Affected Small Entities

We expect U.S. entities affected by the proposed rule to be pharmaceutical manufacturers, possibly including manufacturers of biologic products. Using the North American Industry Classification System (NAICS), we consider these manufacturers to fall under NAICS 325412 "Pharmaceutical Preparation Manufacturing" and NAICS 325414 "Biological Product (Except Diagnostic Manufacturing)." Based on the Small Business Administration's (SBA) 2023 size definitions, SBA considers firms in NAICS 325412 to be small that have no more than 1,300 employees (Ref. [8]). SBA considers firms in NAICS 325414 to be small that have no more than 1,250 employees (Ref. [8]). Based on the 2022 Statistics of U.S. Businesses (SUSB),[5] at least ninety-two percent of firms in NAICS 325412 (1,094 out of 1,179) and eighty-four percent of firms in NAICS 325414 (247 out of 293) are small as defined by SBA.

While most of the firms in these industries thus count as small under the SBA definition, we focus our analysis of impacts in the next section on the smallest firms in the 2022 County Business Patterns and Economic Census dataset (the latest edition of this data that includes revenues),[6] the fifty-nine firms in NAICS 325412 and the eight firms in NAICS 325414 earning no more than $100,000 in annual revenue. These are the firms for whom the proposed rule's costs would be most appreciable as a percentage of revenue. We use publicly available Census data that aggregates firms into bins rather than reporting on individual firms. Nonetheless, all these firms together employ a combined total of under one hundred employees, and hence are among the smallest firms by employment as well as revenue.

B. Description of the Potential Impacts of the Rule on Small Entities

Using the 2022 County Business Patterns and Economic Census dataset, we estimate that the average revenue of a U.S. firm in NAICS 325412 earning no more than $100,000 annually is about $54,390, which we adjust to about $57,732 to reflect the value of the dollar in 2024 using

[5] https://www.census.gov/programs-surveys/susb.html
[6] We use the 2017 dataset because it is the most recent issue containing revenue data at the time of this writing: https://www.census.gov/data/datasets/2017/econ/cbp/2017-cbp.html

the GDP deflator. We estimate that the average revenue of a firm in NAICS 325414 earning no more than $100,000 annually is about $55,750, which we adjust to about $59,176 to reflect the value of the dollar in 2024 again using the GDP deflator. Our high-end estimate of the one-time cost per firm of reading and understanding the rule, $86.34, which we obtain in section II.F.2, thus amounts to about 0.15% of revenue for the smallest U.S. firms. Table 13 below shows estimated gross costs—not accounting for savings—as a percentage of revenue among the smallest potentially affected firms. If considering 3% of annual revenue to be the threshold for significant cost impacts, then firms earning more than $2,878 annually would not be significantly impacted.

Table 13. One-time costs of the proposed rule as percentage of revenue (2024 USD)

	Firms earning under $100,000 annually	Average revenue (2022 USD)	Adjusted for inflation to 2024 dollar value	Reading cost (High estimate, from II.F.1)	Cost as percent of revenue
Pharmaceutical Preparation Manufacturing (NAICS 325412)	59	$54,390	$57,732	$86.34	0.15%
Biological Product (Except Diagnostic) Manufacturing (NAICS 325414)	8	$55,750	$59,176	$86.34	0.15%

With respect to cost savings, we are unsure whether any of these small firms would use DMUs and relocate them. In either industry considered above, if a firm earning no more than $100,000 annually were to operate a single DME with one DMU capable of mobility, the associated $409.65 in savings that we estimate to result from avoided third-party registration service fees in section II.E.2 would amount to approximately 0.7% of revenue, leading to negative net costs.

C. Alternatives to Minimize the Burden on Small Entities

Each of the regulatory alternatives considered, which we describe in section II.I "Analysis of Regulatory Alternatives," similarly imposes a small cost of reading and understanding changes to the registration and listing regulations to address DMEs. We would expect the number of affected small entities to be the same under either alternative as under the proposed rule. However, since the alternatives entail fewer and less substantive changes to registration and listing than the proposed rule, the cost of reading and understanding would most likely also be lower.

IV. **References**

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[6] U.S. Food and Drug Administration, "Requirements for Tobacco Product Manufacturing Practice (Proposed Rule) Preliminary Regulatory Impact Analysis," U.S. Food and Drug Administration, Silver Spring, MD, 2023.

[7] Eastern Research Group, Inc., "Economic Threshold and Regulatory Flexibility Assessment of Proposed Changes to the Current Good Manufacturing Practice Regulations for Manufacturing, Processing, Packing, or Holding Drugs (21 CFR 210 & 211)," Eastern Research Group, Inc., 1995.

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