DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Drug Products or Categories of Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A or 503B of the Federal Food, Drug, and Cosmetic Act

Docket No. FDA-_____-2023-N-0061

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

Economics Staff
Office of Economics and Analysis
Office of Policy, Legislation, and International Affairs
Office of the Commissioner

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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 14094, 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, and 14094 direct us to assess all benefits, costs, and ~~benefits~~transfers of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). ~~We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.~~Rules are "significant" under Executive Order 12866 Section 3(f)(1) (as amended by Executive Order 14094) if they "have an annual effect on the economy of $200 million or more (adjusted every 3 years by the Administrator of the Office of Information and Regulatory Affairs (OIRA) for changes in gross domestic product); or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, territorial, or tribal governments or communities." OIRA has determined that this proposed rule is not a significant regulatory action under Executive Order 12866 Section 3(f)(1).

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because we expect that the proposed rule would have a small, if any, impact on small entities, 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 an assessment of anticipated costs and benefits, 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 one year." The ~~current~~2022 threshold after adjustment for inflation is $177 million, using the ~~most current (~~2022~~)~~ 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. Summary of Costs and Benefits

We evaluated three categories of drug products for this proposed rule. We would place all three of these categories of drug products on the Demonstrable Difficulties for Compounding Lists (DDC lists). ~~We expect that this proposed rule may create benefits for compounders by reducing regulatory uncertainty.~~ Currently, we are not aware of any marketing of compounded drugs in the three proposed categories of human drug products. Therefore, we expect that the proposed rule would only create administrative costs to read and understand the rule for compounders. We seek comments on these assumptions and welcome feedback on any potential benefits that may result from this rulemaking.

In Table 1, we summarize the impacts of the proposed rule. The present value of the costs of the proposed rule would equal $~~3.19~~4.22 million at a 7 percent discount rate and

$~~3.19~~4.22 million at a 3 percent discount rate. The proposed rule would result in annualized costs of $0.~~42~~56 million at a 7 percent discount rate, or $0.~~36~~48 million at a 3 percent discount rate.

Table 1. Summary of Benefits, Costs, and Distributional Effects of the Proposed Rule

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized ($m/year)							
	Annualized Quantified							
	Qualitative	~~Benefits to compounders from reduced regulatory uncertainty.~~						
Costs	Annualized Monetized ($m/year)	$0.~~42~~56	$0.~~38~~51	$0.~~48~~63	2021	7%	10 years	
		$0.~~36~~48	$0.~~33~~43	$0.~~41~~54	2021	3%	10 years	
	Annualized Quantified							
	Qualitative							
Transfers	Federal Annualized Monetized ($m/year)							
		From:			To:			
	Other Annualized Monetized ($m/year)							
		From:			To:			
Effects	State, Local, or Tribal Government: None Small Business: None Wages: None Growth: None							

II. Preliminary Regulatory Impact Analysis

A. Background

Compounders combine, mix, or alter a drug or components of a drug to create a medication tailored to the needs of patients. We call these medications "compounded drug products." The Federal Food, Drug, and Cosmetic Act (FD&C Act) establishes requirements for the manufacture and distribution of drug products in the United States, including requirements for premarket approval of new drug products, labeling, and current good manufacturing practice (CGMP). Section 503A of the FD&C Act sets forth conditions for drug products compounded by State licensed pharmacies, Federal facilities, or licensed physicians and section 503B of the FD&C Act sets forth conditions for drug products compounded by outsourcing facilities. Compounded drug products that meet the conditions in section 503A or section 503B are exempt from some of the requirements for drugs if they meet certain conditions.

One such condition for outsourcing facilities in section 503B is that a compounded drug "is not identified (directly or as part of a category of drugs) on a list published by the Secretary ... of drugs or categories of drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into the account the risks and benefits to patients."[1] A similar condition for State licensed pharmacies, Federal facilities, and licensed physicians in section 503A is that a compounded drug product is "not a drug product identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product."[2] FDA must implement these provisions by regulation.[3] To date, FDA has not issued a regulation to implement these provisions of the FD&C Act.

To implement these provisions, we intend to develop and publish two DDC lists of drug products or categories of drug products that cannot be compounded because they present demonstrable difficulties for compounding, one for compounders covered by 503A and one for outsourcing facilities covered by 503B. Once on a DDC list, these drug products or categories of drug products, if compounded, would not qualify for the exemptions from the provisions of the FD&C Act discussed previously. The proposed rule, if finalized, would establish the criteria to evaluate drug products and categories of drug products for the DDC lists and place three categories of drug products on both of the DDC lists.

B. Need for Federal Regulatory Action

~~Although compounded drugs can serve an important need, they can also pose a higher risk to patients than FDA-approved drugs.~~ Pursuant to sections 503A and 503B of the FD&C Act, FDA is establishing a list of drug products or categories of drug product that cannot be used in compounding under those sections because they present demonstrable difficulties for compounding.

Compounded drug products are not FDA-approved, which means they have not undergone FDA premarket review for safety, effectiveness, and quality. FDA has investigated numerous serious adverse events associated with compounded drug products that were contaminated or otherwise compounded improperly.

~~In addition, licensed~~Licensed pharmacists and licensed physicians who compound drug products in accordance with section 503A are not required to comply with CGMP requirements. Furthermore, FDA does not interact with the vast majority of licensed pharmacists and licensed physicians who compound drug products and seek to qualify for the exemptions under section 503A of the FD&C Act for the drug products that they compound because these compounders are not licensed by FDA and generally do not register their compounding facilities with FDA. Therefore, FDA is often not aware of potential problems with their compounded drug products or compounding practices unless it receives a complaint, such as a report of a serious adverse event or visible contamination.

[1] Section 503B(a)(6)(A) of the FD&C Act.
[2] Section 503A(b)(3)(A) of the FD&C Act.
[3] Sections 503B(c)(1) and 503A(c)(1) of the FD&C Act.

There are greater assurances of quality when drugs are compounded by outsourcing facilities that meet the conditions of section 503B and CGMP requirements than there are for drugs compounded by entities that are not required to comply with CGMP requirements and are not routinely overseen by FDA. However, drug products compounded by outsourcing facilities in accordance with the conditions of section 503B are also exempt from FDA pre-market review requirements and the requirement to be labeled with adequate directions for use.

~~FDA has not established the criteria the Agency would apply to evaluate whether a drug product or category of drug products presents demonstrable difficulties for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug, and the Agency has not yet applied these criteria to add drug products or categories of drug products to the DDC Lists. The absence of a clear regulatory framework for the DDC Lists creates regulatory uncertainty for both compounders seeking to operate in accordance with the conditions of section 503A and outsourcing facilities under section 503B because they do not know how the Agency will apply the criteria to establish the DDC Lists or whether drug products or categories of drug products the Agency has considered for these lists will, in fact, be added.~~

~~FDA has investigated numerous serious adverse events associated with compounded drug products that were contaminated or otherwise compounded improperly.~~

C. Purpose of the Proposed Rule

In this proposed rule, we establish the criteria that we would use to evaluate whether drug products or categories of drug products are difficult to compound under 503A or 503B~~.~~, respectively. These criteria include:

1. Complex formulation;
2. Complex drug delivery mechanism;
3. Complex dosage form;
4. Bioavailability achievement complexity;
5. Compounding process complexity; and
6. Physicochemical or analytical testing complexity.

Using these criteria, we would identify which drug products or categories of drug products to place on the DDC lists. We used these criteria to review three of the nominated categories of drug products for this proposed rule. Based on our review and our consultation with the Pharmacy Compounding Advisory Committee (PCAC), we propose to place these three categories of drug products on the DDC lists. Drug products or categories of drug products that appear on the DDC List for section 503A or the DDC List for section 503B cannot qualify for the statutory exemptions under each section. The following categories of drug products are included in this proposed rule:

1. Drug products produced using hot melt extrusion;
2. Liposome drug products; and
3. Oral solid modified release drug products that employ coated systems.

D. Baseline Conditions

We have limited information about the market for the categories of compounded drug products that we would place on the DDC lists. Moreover, we lack information about the number of entities that might compound these categories of drugs. However, we reviewed ~~any~~ available data and found no evidence of marketing of any of the three categories of human drug products. We request comment on the size of the market for the categories of compounded drug products that we propose to include on the DDC lists.

E. Benefits of the Proposed Rule

~~The proposed rule, if finalized, would establish the criteria that FDA would use to evaluate whether drug products or categories of drug products present demonstrable difficulties for compounding under sections 503A or 503B. By publishing these criteria, the proposed rule, if finalized, may reduce regulatory uncertainty related to the DDC lists. Regulatory uncertainty increases the risk that compounders will begin to develop drugs that FDA would later place on a list of drugs or categories of drugs that the Agency determines cannot be compounded because they present demonstrable difficulties for compounding. Such drugs could present a risk to patients. By establishing the criteria for the DDC Lists and applying the criteria to add three categories of drug products to the DDC Lists, the proposed rule may, once final, reduce regulatory uncertainty because compounders would know how the Agency applies criteria to add drugs or categories of drugs to the DDC Lists, and they would know that the three categories of drugs addressed in this rulemaking cannot be compounded. We request comment on the potential benefits of reduced regulatory uncertainty.~~

We find no evidence of marketing of the three categories of human drug products that we propose to include on the DDC lists. Therefore, we find no additional incremental benefits of proposing to establish the criteria or to place these three categories of human drug on the DDC Lists in this proposed rule. We request comment on any additional potential benefits of this proposed rule.

F. Costs of the Proposed Rule

Because we find no evidence of marketing of the three categories of human drug products that we propose to include on the DDC lists, compounders would not incur costs to discontinue marketing any existing products that the proposed rule would identify as demonstrably difficult to compound under sections 503A or 503B. However, interested compounders would incur small costs to read and understand this proposed rule.

1. Number of Affected Entities

A 2016 report from the Pew Charitable Trusts (Pew) estimated the number of compounding pharmacies for each State and the District of Columbia.[4] To estimate the number of compounding pharmacies, Pew used data from the National Council for Prescription Drug Programs (NCPDP) Pharmacy Provider Database, a comprehensive, proprietary database of pharmacy information.[5] Pew identified 32,407 pharmacies "listing compounding functions," which we use as a proxy for the number of compounding pharmacies. This estimate includes

[4] https://www.pewtrusts.org/-/media/assets/2016/02/national_assessment_of_state_oversight_of_sterile_drug_compounding.pdf

[5] More information about the proprietary Pharmacy Provider Database is available at http://dataq.ncpdp.org/.

both pharmacies specializing in compounding and those performing any compounding. The study notes that, since the NCPDP database does not require pharmacies to list compounding functions, this estimate may be an underestimate.

To better understand the current state of the market for compounding by entities seeking to produce drugs that qualify for the exemptions under section 503A, we accessed updated data from NCPDP as of the end of 2021. We identified 42,885 compounding pharmacies using the same methods as the Pew study.

Outsourcing facilities under Section 503B of the FD&C register with FDA annually. We use this registration data to determine the number of outsourcing facilities in 2021. We identified 79 unique compounders registered with FDA as outsourcing facilities in 2021.

2. Costs to Read and Understand the Rule

Given the length of the preamble (approximately 11,000 words) and an average reading speed between 200 and 250 words per minute[6], we estimate that it would take each compounder between 0.73 hours (11,000 words ÷ 250 words per minute ÷ 60 minutes per hour) and 0.92 hours (11,000 words ÷ 200 words per minute ÷ 60 minutes per hour) to read and understand the proposed rule. From the Bureau of Labor Statistics' 2021 National Occupational Employment and Wage Estimates[7], the average wage for a pharmacist is $60.31 per hour. Assuming overhead and benefits equal 100 percent of the annual wage, the fully loaded cost of labor for a pharmacist is $120.62 per hour ($60.31 × (1 + 100%)). Therefore, we estimate that each compounder would incur between $88.45 (0.73 hours × $120.62 per hour) and $110.57 (0.92 hours × $120.62 per hour) in administrative costs to read and understand the rule.

We estimate that there are ~~32,486~~42,964 compounding pharmacies and outsourcing facilities in the United States (~~32,407~~42,885 compounding pharmacies + 79 outsourcing facilities). Because this proposed rule includes criteria that we would use to evaluate drug products and categories of drug products for inclusion on the DDC lists, we assume that all ~~32,486~~42,964 compounders would incur costs to read and understand the rule. The total one-time cost to read and understand the rule would range from $~~2.87~~3.80 million (~~32,486~~42,964 compounders × $88.45 per compounder) to $~~3.59~~4.75 million (~~32,486~~42,964 compounders × $110.57 per compounder).

We assume that firms would read and understand the proposed rule during the first year after the publication of the final rule. Therefore, over 10 years, the annualized costs would range from $0.~~38~~53 million to $0.~~48~~63 million at a 7 percent discount rate and from $0.~~33~~43 million to $0.~~41~~54 million at a 3 percent discount rate.

We request comment on any additional costs of this proposed rule.

III. Initial Small Entity Analysis

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because firms would only

[6] https://aspe.hhs.gov/reports/guidelines-regulatory-impact-analysis
[7] Available at https://www.bls.gov/oes/current/oes_nat.htm.

incur small costs to read and understand the rule of between $88.45 per firm and $110.57 per firm, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document, serves as the Initial Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.