DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

REPEAL OF REGULATION REQUIRING AN APPROVED NEW DRUG APPLICATION FOR DRUGS STERILIZED BY IRRADIATION

Docket No. FDA-2017-N-6924

Final Regulatory Impact Analysis

Final Regulatory Flexibility Analysis

Unfunded Mandates Reform Act Analysis

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I. Introduction and Summary

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, 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 costs and benefits 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). Executive Order 13771 requires that the costs associated with significant new regulations "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations." We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the final rule will affect few entities and the net effect will be cost savings to affected firms, we certify that the final 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 issuing "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 threshold after adjustment for inflation is $154 million, using the most current (2018) Implicit Price Deflator for the Gross

Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

The final rule will repeal the irradiation regulation (21 CFR § 310.502(a)(11)), a regulation that provides that any drug sterilized by irradiation is a new drug. Repealing this regulatory provision will mean that over-the-counter (OTC) drugs marketed pursuant to the OTC Drug Review that are generally recognized as safe and effective (GRASE), that are not misbranded, and that comply with all applicable regulatory requirements may be legally marketed without an FDA-approved new drug application (NDA) or abbreviated new drug application (ANDA), even if the drugs are sterilized by irradiation. We consider this regulation as outdated and unnecessary because we no longer conclude that drugs sterilized by irradiation are necessarily new drugs. The technology of controlled nuclear radiation for the sterilization of drugs is now well understood. In addition, drugs marketed pursuant to the OTC Drug Review must be manufactured in compliance with our Current Good Manufacturing Practice (CGMP) regulations. Appropriate and effective sterilization of drugs, including sterilization by irradiation, is adequately addressed by the CGMP requirements.

The irradiation regulation requires manufacturers of OTC drugs to submit an NDA or an ANDA to market a drug if it is sterilized by irradiation. Given the availability of other forms of sterilization, we expect that many manufacturers of OTC drugs use alternative forms of sterilization rather than incur the expense of an NDA or ANDA. Consequently, we assume that the final rule will have zero costs and zero benefits for firms that market OTC drugs manufactured with alternative forms of sterilization. For firms manufacturing OTC drugs that would have submitted an NDA or ANDA in the absence of this deregulatory action, we assume

the final rule will generate net benefits in the form of costs savings. Table 1 summarizes our estimate of the annualized costs and benefits of the final rule.

Table 1. Summary of Benefits, Costs and Distributional Effects of the Rule ($ million)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $millions/year	$0.06	$0.05	$0.07	2018	7%	10 years	Benefits are cost savings
		$0.05	$0.05	$0.06	2018	3%	10 years	Benefits are cost savings
	Annualized Quantified				2018	7%	10 years	
					2018	3%	10 years	
	Qualitative							
Costs	Annualized Monetized $millions/year	$0.00	$0.00	$0.00	2018	7%	10 years	Less than $100
		$0.00	$0.00	$0.00	2018	3%	10 years	Less than $100
	Annualized Quantified				2018	7%	10 years	
					2018	3%	10 years	
	Qualitative							
Transfers	Federal Annualized Monetized $millions/year	$0.16	$0.16	$0.16	2018	7%	10 years	User Fee
		$0.14	$0.14	$0.14	2018	3%	10 years	User Fee
		From:			To:			
	Other Annualized Monetized $millions/year				2018	7%	10 years	
					2018	3%	10 years	
		From:			To:			
Effects	State, Local or Tribal Government: None Small Business: None Wages: None Growth: None							

In line with Executive Order 13771, in Table 2 we estimate present and annualized values of costs and cost savings over an infinite time horizon. With a 7 percent discount rate, the estimated annualized net cost-savings equal $0.06 million in 2016 dollars over an infinite horizon. Based on these cost-savings this final rule would be considered a deregulatory action under Executive Order 13771.

Table 2. Executive Order 13771 Summary (in $ Millions 2016 dollars, over an infinite horizon)

	Primary (7%)	Lower Bound (7%)	Upper Bound (7%)	Primary (3%)	Lower Bound (3%)	Upper Bound (3%)
Present Value of Costs	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Present Value of Cost Savings	$0.88	$0.75	$1.00	$1.75	$1.50	$8.01
Present Value of Net Costs	**($0.88)**	**($0.75)**	**($1.00)**	**($1.75)**	**($1.50)**	**($2.00)**
Annualized Costs	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Annualized Cost Savings	$0.06	$0.05	$0.28	$0.05	$0.05	$0.24
Annualized Net Costs	**($0.06)**	**($0.05)**	**($0.07)**	**($0.05)**	**($0.05)**	**($0.06)**

Note: Net costs are calculated as costs minus cost savings. Values in parentheses denote net negative costs (i.e. cost-savings).

We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule.

C. Comments on the Proposed Rule

We published a proposed rule on September 12, 2018 (83 FR 46121), that would remove the regulation that requires drugs sterilized by irradiation to have an approved new drug application before a sponsor can legally market the drug. We received five public comments on the proposed rule. All comments were generally supportive of the proposed rule. None of the comments directly address the Preliminary Regulatory Impact Analysis (PRIA) that accompanied the proposed rule. Some of the comments mention that the proposed rule would likely reduce costs or regulatory burden with no increase in public health risk. Those positions agree with the conclusions of the PRIA.

D. Summary of Changes

We retain the cost and benefit model used in the PRIA for this Final Regulatory Impact Analysis, with one small change. We reduce the upper-bound estimate of the cost to prepare a new drug application to align it with the uncertainty surrounding the lower-bound estimate. We also update the dollar figures reported for the primary cost model and Regulatory Flexibility Act into the most recent year available (2018).

II. Final Regulatory Impact Analysis

A. Background and Purpose of the Rule

21 CFR 310.502(a) sets forth a list of drugs that have been determined by rulemaking procedures to be "new drugs" within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Included on the list are drugs that are sterilized by irradiation (§ 310.502(a)(11) (21 CFR 310.502(a)(11)). Because this regulation reflected our determination at the time of promulgation that the drugs on the list are "new drugs," a manufacturer of a drug sterilized by irradiation had to submit an NDA or ANDA, and we had to approve the application before the drug could be marketed legally. Thus, the irradiation regulation required that an OTC drug product sterilized by means of irradiation have an approved NDA or ANDA before a manufacturer could introduce the OTC product into interstate commerce.

We are withdrawing the irradiation regulation because we no longer conclude that drugs sterilized by irradiation are necessarily new drugs. Unlike in 1955, when the irradiation regulation was first published, the technology for controlled nuclear radiation to sterilization drugs is now well understood. Also, in 1955, neither the OTC Drug Review nor the CGMP requirements existed. Among the general conditions pertaining to drugs marketed under the OTC Drug Review is the requirement that OTC drugs be manufactured in compliance with CGMPs.

The CGMP requirements encompass sterilization of drugs, including by radiation. Therefore, we can revoke the irradiation regulation and manufacturers will still be obligated to ensure that, when they use radiation for sterilization: (1) the drug products are sterile; and (2) the use of radiation does not have a detrimental effect on the drug products' identity, strength, quality, purity, or stability.

B. Market Failure Requiring Federal Regulatory Action

This final rule will correct the institutional failure created by our outdated and unnecessary regulation that requires manufacturers of an irradiated OTC drug product to submit and obtain approval of a NDA or ANDA before they can market their OTC drug product. This institutional failure causes firms to incur additional development costs without any additional public health benefits. Because these additional costs can act as a barrier to entry for manufacturers that choose to use irradiation to sterilize their OTC drug products, federal action is required to formally remove the burdensome regulatory requirement for an NDA or an ANDA.

C. Benefits and Costs of the Rule

1. Number of Affected Entities

The affected entities covered by this final rule are the drug manufacturers of the OTC products that would have had to submit an NDA or an ANDA only because of the irradiation regulation. No entities have submitted an NDA or an ANDA under the current regulation since 2011. However, one entity that petitioned us to remove the rule might have submitted an NDA or ANDA in the absence of this deregulatory action. For this analysis, therefore, we assume that the final rule will affect only one entity every 10 years.

2. Potential Social Costs

Because the preapproval process is superfluous to ensure the safety or effectiveness of OTC drugs sterilized by irradiation that could otherwise be legally marketed pursuant to the OTC Drug Review, we estimate that the public would not sustain any additional avoidable risks of injury by removing the NDA and ANDA requirement. In addition, the final rule will impose very minor one-time costs to learn the requirements of the rule upon the affected entity. The Department of Health and Human Services (HHS) guidance for estimating the cost is based on the time it takes a manager to read the preamble at a reading speed of 200 to 250 words per minute (Ref. 1). The preamble has approximately 2,800 words. To estimate the cost of a manager's time, we use the median hourly wage in the pharmaceutical and medical manufacturing industry for a General and Operations Manager (North American Industry Classification, NAICS, code 325400) from the Bureau of Labor Statistics (BLS) May 2018 National Occupational Employment and Wage Estimates for General and Operations managers Occupation code 11-1021, which is $68.05 (Ref. 2). To account for benefits and overhead, we double this value to roughly $136.10 (= $68.05 x 2). We estimate the one-time cost to learn the requirements of the rule ranges from about $25 to $32.

3. Cost Savings Benefits

The final rule will reduce the regulatory burden to manufacturers of certain OTC drugs because it will mean that OTC drugs marketed pursuant to the OTC Drug Review that are GRASE, that are not misbranded, and that comply with all applicable regulatory requirements may be legally marketed without an FDA-approved NDA or ANDA, even if the drugs are sterilized by irradiation. We calculate the cost saving benefits as the avoided 1) one-time cost to prepare and review an NDA or ANDA, and 2) one-time cost of delays in the production and sale of their products while the affected manufacturer waits for approval of their application.

As our primary estimate for the one-time cost to prepare a new drug application, we use our paperwork estimate of 1,921 hours as described in the Federal Register (82 Fed. Reg. 58403, Dec. 12, 2017). We then multiply the total hours by the average industry wage rate of $136.10, for a one-time total cost of approximately $261,448 per NDA. We assume that as a lower bound estimate, the number of hours would be 75 percent of our primary estimate or 1,441 hours, for a total cost of approximately $196,086 per NDA. We assume that as an upper bound estimate, the number of hours would be 25 percent larger than our primary estimate or 2,401 hours, for a total cost of approximately $326,810 per NDA.

The lost sales revenue from the longer NDA or ANDA approval process depends on the production and distribution of an affected product. The most recent NDA for the irradiation of a product, NDA 22305, was approved on September 1, 2011, approximately 11 months after the application submission (Ref. 3), which suggests some lost sales revenue. However, we lack data that allows us to quantify the magnitude of the lost sales revenue during the NDA approval process.

4. FDA Review Time Savings

The final rule should also reduce the time that we spend reviewing and responding to the NDA or ANDA submission. The annual savings should roughly equal the reduced time that our scientists spend on their review multiplied by their hourly wage rate. We estimate that our scientists spend approximately 1,500 hours reviewing and responding to each NDA or ANDA based on data collected by the Agency's Regulatory Information Management System (RIMS) (Ref. 4). Using FDA's Fully Loaded Full Time Employee (FTE) Cost Model (Domestic) for FY 2016, we estimate that the total cost including pay, information and management technology, general and administrative overhead, and rent for a new drug reviewer is $273,737 for an

average of 2,080 hours worked per year, which equals $132 per hour. We increase this by 4.20 percent to adjust for 2018 wage estimates, resulting in an estimate of $137 per hour. We estimate that our review time savings would be approximately $205,000 (= 1,500 hours x $137/ hr.)

5. Summary of Costs and Benefits

Table 3 shows the one-time and annualized costs and benefits of the final rule over 10 years. We estimate that the final rule will generate net benefits in the form of cost savings.

Table 3. Summary of the Primary Estimate of Costs and Benefits of the Proposed Rule ($ million)

	One-Time	Annualized Over 10 Years at 7%[1]	Annualized Over 10 Years at 3%[1]
Costs[1]	$0.00	$0.00	$0.00
Benefits[2]	$0.47	$0.06	$0.05

[1] Annualized one-time costs for industry total less than $100.
[2] The benefits of this final rule are cost savings.

D. Distributional Effects

Manufacturers of OTC drugs that only would have needed to submit an NDA or an ANDA because they irradiate their products would also have incurred the cost of a user fee. Under the final rule, however, manufacturers will no longer pay this user fee to FDA. To estimate the distributional effects of the final rule, we again use data from the most recent NDA for irradiation -- NDA 22305 (Ref. 3) -- to determine the user fee schedule. This product has a single active ingredient and did not include reports of clinical investigations. Consequently, we use the most recent Prescription Drug User Fee Act (PDUFA) fee schedule for an NDA without clinical data to estimate the user fee in 2018 of $1,210,748 (Ref. 5). However, regulatory actions that cause only income transfers would not be considered cost savings under EO 13771.

III. Final Small Entity Analysis

We note that the current regulation and costs associated with submission of an NDA or

ANDA may have created a barrier to entry for small entities. Although we lack data to estimate the impact that revoking the regulation would have on small entities, we expect that it could encourage more small entities to market irradiated OTC products.

We examined the economic impact of this final rule as required by the Regulatory Flexibility Act. If a rule will have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. We certify that the final rule will not have a significant economic impact on a substantial number of small entities. This analysis, together with other relevant sections of this document, serves as the final regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

IV. 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. We have verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. Guidelines for Regulatory Impact Analysis, HHS September 2016. https://aspe.hhs.gov/system/files/pdf/242926/HHS_RIAGuidance.pdf
2. Bureau of Labor Statistics. National Occupational Employment and Wage Estimates. Occupational Employment Statistics, General and Operations Manager (North American Industry Classification, NAICS, code 325400), May 2018.

https://www.bls.gov/oes/2018/may/naics4_325400.htm

3. Center for Drug Evaluation and Research NDA Application Number 022305 Orig1s000 Administrative and Correspondence Documents https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022305Orig1s000Admincorres.pdf accessed on August 14, 2017.
4. Email correspondence from FDA RIMS staff.
5. FDA Prescription Drug User Fee Act (PDUFA) https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm accessed 08-14-2017.

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For Consideration, Docket No. FDA-2017-N-6924 is submitted.

Under the following from 2019, the federal government repealed labeling of drugs given it considered this regulation as outdated and unnecessary because it is no longer concludee that drugs sterilized by irradiation are necessarily new drugs. They are considered GRASE.

The final rule will repeal the irradiation regulation (21 CFR § 310.502(a)(11)), a regulation that provides that any drug sterilized by irradiation is a new drug. Repealing this regulatory provision will mean that over-the-counter (OTC) drugs marketed pursuant to the OTC Drug Review that are generally recognized as safe and effective (GRASE), that are not misbranded, and that comply with all applicable regulatory requirements may be legally marketed without an FDA-approved new drug application (NDA) or abbreviated new drug application (ANDA), even if the drugs are sterilized by irradiation. We consider this regulation as outdated and unnecessary because we no longer conclude that drugs sterilized by irradiation are necessarily new drugs. The technology of controlled nuclear radiation for the sterilization of drugs is now well understood. In addition, drugs marketed pursuant to the OTC Drug Review must be manufactured in compliance with our Current Good Manufacturing Practice (CGMP) regulations. Appropriate and effective sterilization of drugs, including sterilization by irradiation, is adequately addressed by the CGMP requirements.