

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

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

Economics Staff
Office of Planning
Office of Policy, Planning, Legislation and Analysis
Office of the Commissioner

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Table of Contents

| | |
|---|----|
| I. Introduction and Summary | 3 |
| A. Introduction..... | 3 |
| B. Summary..... | 4 |
| II. Economic Impact Analysis | 6 |
| A. Background..... | 6 |
| B. Market Failure Requiring Federal Regulatory Action | 7 |
| C. Benefits and Costs | 7 |
| 1. Number of Affected Entities..... | 7 |
| 2. Potential Social Costs..... | 8 |
| 3. Cost Savings Benefits..... | 8 |
| 4. FDA Review Time Savings | 9 |
| 5. Summary of Costs and Benefits | 10 |
| D. Distributional Effects..... | 10 |
| III. Preliminary Small Entity Analysis | 10 |
| IV. References..... | 11 |

I. Introduction and Summary

A. Introduction

We have examined the impacts of the proposed rule under Executive Order (EO) 12866, EO 13563, EO 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). EOs 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). EO 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 proposed rule is not a significant regulatory action as defined by EO 12866. This proposed rule, if finalized, is considered an EO 13771 deregulatory action.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because few entities will be affected and the net effect will be cost savings to affected firms, we propose to certify that the proposed rule, if finalized, 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 \$150 million, using the most current (2017) 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.

We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full analysis of economic impacts is available in the docket for this proposed rule (Ref. 8) and at

<https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

B. Summary

The proposed rule, if finalized, will repeal 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.

Sponsors of drugs that are not covered by an OTC monograph must submit an NDA or an ANDA regardless of the type of sterilization they decide to use. Because of the irradiation regulation, sponsors of drugs that are covered by an OTC monograph and could otherwise reach the market without submission of an NDA or ANDA must nonetheless submit NDAs or ANDAs to market their drugs if they sterilize their drugs via irradiation. Given the availability of other

forms of sterilization, we expect that many manufacturers of such drugs use alternative forms of sterilization rather than incur the expense of an NDA or ANDA. Consequently, we assume that the proposed rule, if finalized, will have zero costs and zero benefits for firms that market OTC drugs manufactured with alternative forms of sterilization. For firms manufacturing such drugs that would have submitted an NDA or ANDA in the absence of this deregulatory action, we assume the rule will generate net benefits in the form of costs savings. Table 1 summarizes our estimate of the annualized costs and benefits of the 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 | \$0.28 | 2016 | 7% | 10 years | Benefits are cost savings |
| | | \$0.05 | \$0.04 | \$0.24 | 2016 | 3% | 10 years | Benefits are cost savings |
| | Annualized Quantified | | | | 2016 | 7% | 10 years | |
| | | | | | 2016 | 3% | 10 years | |
| | Qualitative | | | | | | | |
| Costs | Annualized Monetized \$millions/year | \$0.00 | \$0.00 | \$0.00 | 2016 | 7% | 10 years | Less than \$100 |
| | | \$0.00 | \$0.00 | \$0.00 | 2016 | 3% | 10 years | Less than \$100 |
| | Annualized Quantified | | | | 2016 | 7% | 10 years | |
| | | | | | 2016 | 3% | 10 years | |
| | Qualitative | | | | | | | |
| Transfers | Federal Annualized Monetized \$millions/year | \$0.14 | \$0.14 | \$0.14 | 2016 | 7% | 10 years | User Fee |
| | | \$0.12 | \$0.12 | \$0.12 | 2016 | 3% | 10 years | User Fee |
| | From: | | | | To: | | | |
| | Other Annualized Monetized \$millions/year | | | | 2016 | 7% | 10 years | |
| | | | | | 2016 | 3% | 10 years | |
| | From: | | | | To: | | | |

| Category | Primary Estimate | Low Estimate | High Estimate | Units | | | Notes |
|----------|--|--------------|---------------|--------------|---------------|----------------|-------|
| | | | | Year Dollars | Discount Rate | Period Covered | |
| Effects | State, Local or Tribal Government: None Small Business: None Wages: None Growth: None | | | | | | |

This proposed rule, if finalized, will 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 take this regulatory action as part of our retrospective review to promote improvement and innovation. Because the proposed rule, if finalized, will repeal an outdated regulation and generate net cost savings, we consider this action a deregulatory action under EO 13771. Table 2 presents a summary of the EO 13771 impacts of the proposed rule over an infinite horizon. For this estimate, we assume that one sponsor will benefit from this deregulatory action every 10 years.

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 | \$0.97 | \$0.83 | \$4.37 | \$1.84 | \$1.58 | \$8.30 |
| Present Value of Net Costs | (\$0.97) | (\$0.83) | (\$4.37) | (\$1.84) | (\$1.58) | (\$8.30) |
| Annualized Costs | \$0.00 | \$0.00 | \$0.00 | \$0.00 | \$0.00 | \$0.00 |
| Annualized Cost Savings | \$0.07 | \$0.06 | \$0.31 | \$0.06 | \$0.05 | \$0.25 |
| Annualized Net Costs | (\$0.07) | (\$0.06) | (\$0.31) | (\$0.06) | (\$0.05) | (\$0.25) |

II. Economic Impact Analysis

A. Background

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 is “[s]terilization of drugs by irradiation” (§ 310.502(a)(11) (21 CFR 310.502(a)(11))). Because this regulation reflects an FDA determination that the drugs on the list are

“new drugs,” an NDA or ANDA must be submitted and approved by FDA before they can be marketed legally. For a non-prescription drug that could otherwise be legally marketed without an approved NDA or ANDA in effect pursuant to the OTC Drug Review, the effect of § 310.502(a)(11) is that all drug products sterilized by means of irradiation must have an approved NDA or ANDA before the manufacturer can introduce the OTC product into interstate commerce.

FDA is withdrawing § 310.502(a)(11) because the Agency no longer concludes that drugs sterilized by irradiation are necessarily new drugs. Unlike in 1955, when the statement now reflected in § 310.502(a)(11) was first published, the technology for controlled nuclear radiation for the sterilization of 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, § 310.502(a)(11) can be revoked and manufacturers will still be obligated to ensure that, if they use radiation: (1) the drug products that they purport to be sterile are in fact sterile; and (2) their use of radiation does not have a detrimental effect on their drug products’ identity, strength, quality, purity, or stability.

B. Market Failure Requiring Federal Regulatory Action

This proposed rule, if finalized, 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

1. Number of Affected Entities

The affected entities covered by this proposed rule are the drug manufacturers of the OTC products that would have had to submit an NDA or an ANDA only because of § 310.502(a)(11). 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 proposed rule, if finalized, 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 proposed rule, if finalized, 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 6,600 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 2016 National Occupational Employment and Wage Estimates for General and Operations managers Occupation code 11-1021, which is approximately \$68.45 (Ref. 2). To account for benefits and overhead, we double this value to roughly \$136.90 ($= \68.45×2). We estimate the one-time cost to learn the requirements of the rule ranges from about \$120 to \$150.

3. Cost Savings Benefits

The proposed rule, if finalized, would reduce the regulatory burden to manufacturers of OTC drugs that can otherwise currently be marketed pursuant to the OTC Drug Review but that must submit NDAs or ANDAs because they sterilize the drugs via 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, 79 FR 55801 (Sept. 17, 2014) (Ref. 3). We then multiply the total hours by the average industry wage rate of \$136.90, for a one-time total cost of approximately \$262,985 per NDA. We assume that as a lower bound estimate, the number of hours would be 75 percent of our primary estimate or 1,440 hours, for a total cost of approximately \$197,136 per NDA. As our upper bound estimate, we use the estimate created for the Office of Management and Budget (OMB) Information Collection Supporting Statement 0910-0338 of \$1,878,964, or approximately \$1,900,000 (Ref. 4).

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. 5), 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 proposed rule, if finalized, 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. 6). 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 estimate that our review time savings would be approximately \$200,000 (= 1,500 hours x \$132/ hr.)

5. Summary of Costs and Benefits

Table 3 shows the one-time and annualized costs and benefits of the proposed rule over 10 years. We estimate that the proposed rule, if finalized, would 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 | \$0.46 | \$0.06 | \$0.05 |

¹ Annualized one-time costs for industry total less than \$100.

² The benefits of this proposed rule are cost savings.

D. Distributional Effects

Manufacturers of OTC drugs that only need to submit an NDA or an ANDA because they irradiate their products would also incur the cost of a user fee. Under the proposed rule, however, manufacturers would no longer pay this user fee to FDA. To estimate the distributional effects of the proposed rule, we again use data from the most recent NDA for irradiation -- NDA 22305 (Ref. 6) -- 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 2017 of \$1,019,050 (Ref. 7). However, regulatory actions that cause only income transfers would not be considered cost savings under EO 13771.

III. Preliminary Small Entity Analysis

We note that the current regulation and costs associated with submission of a 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 proposed 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 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, together with other relevant sections of this document, serves as the preliminary 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 2014, Revised Draft with May 2015 Update.
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 2015.
3. 79 FR 55801 (Sept. 17, 2014).
4. OMB Information Collection Supporting Statement 0910-0338.
5. Center for Drug Evaluation and Research NDA Application Number 022305
Orig1s000 Administrative and Correspondence Documents
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022305Orig1s000Amdincorres.pdf accessed on August 14, 2017.

6. Email correspondence from FDA RIMS staff.
7. FDA Prescription Drug User Fee Act (PDUFA)

<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

accessed 08-14-2017.