4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. FDA-2017-N-6924]

RIN 0910-AH47

Repeal of Regulation Requiring an Approved New Drug Application for Drugs Sterilized by Irradiation

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing to repeal a regulation that requires an FDA-approved new drug application (NDA) or abbreviated new drug application (ANDA) for any drug product that is sterilized by irradiation (the irradiation regulation). Repealing the irradiation regulation would mean that over-the-counter (OTC) drug products that are generally recognized as safe and effective, that are not misbranded, and that comply with all applicable regulatory requirements can be marketed legally without an NDA or ANDA, even if they are sterilized by irradiation. FDA is proposing to take this action because the irradiation regulation is out of date and unnecessary. The technology of controlled nuclear radiation for sterilization of drugs is now well understood, and our regulations require that OTC drugs be manufactured in compliance with current good manufacturing practices (CGMPs). Appropriate and effective sterilization of drugs, including by irradiation, is adequately addressed by the CGMP requirements. This action is part of FDA's implementation of Executive Orders (EOs) 13771 and 13777. Under these EOs, FDA is comprehensively

reviewing existing regulations to identify opportunities for repeal, replacement, or modification that will result in meaningful burden reduction while allowing the Agency to achieve our public health mission and fulfill statutory obligations.

DATES: Submit either electronic or written comments on the proposed rule by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The https://www.regulations.gov electronic filing system will accept comments until midnight Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact

information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

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

Instructions: All submissions received must include the Docket No. FDA-2017-N-6924 for "Repeal of Regulation Requiring an Approved New Drug Application for Drugs Sterilized by Irradiation." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS

CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Sudha Shukla, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5198, Silver Spring, MD 20993-0002, 301-796-3345.

SUPPLEMENTARY INFORMATION:

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I. Executive Summary

This proposed rule would repeal the irradiation regulation, which provides that any drug sterilized by irradiation is a new drug. This action, if finalized, would mean that OTC drugs marketed pursuant to the OTC Drug Review that are generally recognized as safe and effective, that are not misbranded, and that comply with all applicable regulatory requirements can be marketed legally without an FDA-approved NDA or ANDA, even if the drugs are sterilized by irradiation. FDA is taking this action because the Agency no longer concludes that drugs

sterilized by irradiation are necessarily new drugs. The technology of controlled nuclear radiation for sterilization of drugs is now well understood. In addition, drugs that are marketed pursuant to the OTC Drug Review must be manufactured in compliance with CGMPs. Appropriate and effective sterilization of drugs, including by irradiation, is adequately addressed by the CGMP requirements. Repealing the irradiation regulation would eliminate a requirement that is no longer necessary, and will not diminish public health protections.

The estimated one-time costs of this rule range from $120 to $150. Avoiding the unnecessary preparation and review of a premarket drug application will generate an estimated one-time cost savings that range from about $395,000 to $2,076,000. Over 10 years with a 7 percent discount rate, the annualized net cost savings range from $0.05 million to $0.28 million, with a primary estimate of $0.06 million; with a 3 percent discount rate, the annualized net cost savings range from $0.04 million to $0.24 million, with a primary estimate of $0.05 million. Over an infinite horizon, we assume that one sponsor will benefit from this deregulatory action every 10 years; the present value of the net cost savings over the infinite horizon range from $0.83 million to $4.37 million with a 7 percent discount rate and from $1.58 million to $8.30 million with a 3 percent discount rate.

II. Background and Discussion

On February 24, 2017, EO 13777, "Enforcing the Regulatory Reform Agenda" (https://www.gpo.gov/fdsys/pkg/FR-2017-03-01/pdf/2017-04107.pdf) was issued. One of the provisions in the EO requires Agencies to evaluate existing regulations and make recommendations to the Agency head regarding their repeal, replacement, or modification, consistent with applicable law. As part of this initiative, FDA is proposing to repeal the irradiation regulation as specified in this rule.

In addition, in a citizen petition dated August 14, 2014, Richard O. Wood of The Wood Burditt Group LLC requested that the irradiation regulation be revoked. FDA has responded to Mr. Wood's citizen petition. A copy of the response is available at: https://www.regulations.gov under Docket No. FDA-2014-P-1784.

A. The History of the Irradiation Regulation

In the November 29, 1955, issue of the *Federal Register*, FDA issued a statement of interpretation relating to the sterilization of drugs by irradiation (20 FR 8747 to 8748).[1] In the statement, FDA explained that there was an interest in the utilization of newly developed sources of radiation for the sterilization of drugs. The Agency went on to state that it was necessary in the interest of protecting the public health to establish by adequate investigations that the irradiation treatment does not cause the drug to become unsafe or otherwise unsuitable for use. For this reason, all drug products sterilized by irradiation would be regarded as new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which would mean that an effective new drug application would be required for such products.

In 1996, FDA proposed to revise the statement and consolidate it with similar provisions into a single list of drugs that have been determined by previous rulemaking procedures to be new drugs within the meaning of section 201(p) of the FD&C Act (61 FR 29502 at 29503 to 29504 (June 11, 1996)). The Agency proposed to remove any existing background information describing the Agency's basis for determination of new drug status from the regulatory text.

In 1997, FDA finalized these provisions, now located in 21 CFR 310.502, entitled "Certain drugs accorded new drug status through rulemaking procedures." (62 FR 12084 at

[1] Available at: https://www.loc.gov/item/fr020231/. A month later, this provision was included at § 3.45 in the republication of chapter 21 of the Code of Federal Regulations in the *Federal Register*. See 20 FR 9525 at 9554 (December 20, 1955), available at: http://cdn.loc.gov/service/ll/fedreg/fr020/fr020246/fr020246.pdf. In 1975, FDA republished and re-codified the rule at 21 CFR 200.30. See 40 FR 13996 at 13997 (March 27, 1975), available at: https://www.loc.gov/item/fr040060/.

12084 (March 14, 1997).) Paragraph 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 FD&C Act. Included on the list is sterilization 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, if the drug is sterilized by irradiation, an approved NDA or ANDA is necessary.

B. Sterilization by Irradiation

Since the paragraph now reflected at § 310.502(a)(11) was published in 1955, the technology of controlled nuclear radiation for sterilization of drugs has become well understood. Gamma ray irradiation has been recognized as a method of sterilizing drug products for half a century (Refs. 1 and 2). Electron beam and x-ray irradiation are also recognized methods for sterilizing drugs (Ref. 1).

Information and data on whether a particular drug can safely and effectively be sterilized by irradiation are available in the scientific literature (Ref. 1). The United States Pharmacopeial Convention (USP) has provided guidance on irradiation sterilization of drug products since 1965 (Refs. 1 and 3). This includes chapter <1229> on "Sterilization of Compendial Articles," which sets forth principles that may be applied to the sterilization of compendial and non-compendial drug products, and chapter <1229.10> on "Radiation Sterilization," which sets forth guidelines on validation of sterilization by irradiation (Refs. 3 and 4). The American National Standards Institute, the Association for the Advancement of Medical Instrumentation, ASTM International,

and the International Organization for Standardization (ISO) have also published standards on the irradiation of medical products, including drugs (Ref. 1). ISO standard 11137, which sets forth several methods that can be used to determine the appropriate radiation dose for health care products, was first published in 1984[2] (Ref. 1).

USP chapter <1229.10> states that the methods set forth in ISO 11137 typically guide the choice of radiation dose (Ref. 3). Relevant factors include a drug's pre-sterilization level of microbial contamination (sometimes referred to as its bioburden) and the desired sterility assurance level (Ref. 1). Once the dose is selected, USP General Chapter <1229.10> states that all materials exposed to radiation, especially the drug product and its primary container, should be evaluated for immediate and long-term effects, and "[p]roduct stability, safety, and functionality should be confirmed over the product's intended use period" (Ref. 3). Among the advantages of sterilizing drug products by irradiation is that due to radiation's high penetrability, drug products can be irradiated after they are placed in their final containers (Ref. 1). Known as terminal sterilization, this provides a greater degree of sterilization assurance than aseptic processing and, where feasible, its use is preferable to relying solely on aseptic processing to ensure sterility (Ref. 5). Other advantages to irradiation sterilization of drugs include low chemical reactivity; the very low rise in temperature associated with radiation, which allows for its use on heat-sensitive products; that irradiation sterilization has fewer process variables than

[2] ISO 11137-1 specifies standards for the development, validation, and routine control of a radiation sterilization process for medical devices, while ISO 11137-2 specifies dose establishment and dose audit methods and defines product family approaches for dose establishment and dose audits. Additional target sterilization doses are covered in ISO Technical Information Report (TIR) 13004. Neither ISO 11137-2 nor TIR 13004 is explicitly limited to medical devices. In addition, both ISO 11137-2 and ISO TIR 13004 reference ISO 11137-1 as "indispensable for the application of this document." This implies that the concepts in ISO 11137-1 may be applied to sterilization of drug products.

other methods, which translates into fewer sterility rejections; and that radiation does not leave behind any sterilant residuals (Refs. 1 and 6).

C. The OTC Drug Monograph System and Current Good Manufacturing Practices

The OTC Drug Review was established to evaluate the safety and effectiveness of OTC drug products marketed in the United States before May 11, 1972. As set forth in 21 CFR 330.10, it is a multiphase public rulemaking process (each phase requiring a *Federal Register* publication) resulting in the establishment of monographs for OTC therapeutic drug classes. OTC drug monographs, which can be found in Title 21, chapter I, subchapter D of the Code of Federal Regulations, cover acceptable ingredients, doses, formulations, other conditions, and labeling for certain OTC drugs. A company can legally make and market an OTC product that meets each of the conditions contained in an applicable monograph and, in addition, each of the general conditions set forth in § 330.1. Among the general conditions that apply to all drug products marketed under the OTC Drug Review is the requirement set forth in § 330.1(a) that they be manufactured in compliance with current good manufacturing practices, as established by parts 210 and 211 of this chapter. The CGMP requirements in parts 210 and 211 encompass sterilization, including by irradiation.[3]

In 1955, when the determination with respect to drugs sterilized by irradiation (now reflected in § 310.502(a)(11)) was made, neither the OTC drug monograph system nor the CGMP requirements existed. The authorizing legislation that the CGMP regulations implement, section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)), was enacted in 1962 (*Drug*

[3] We note that sterilization is not generally a condition specifically covered by OTC monographs. Currently, the monograph for ophthalmic drug products at 21 CFR part 349 is the only monograph that incorporates a sterility condition. There are, however, OTC products covered by a monograph or tentative final monograph that are not required to be sterile, but which manufacturers may choose to sterilize. These may include consumer and healthcare antiseptics, such as consumer hand washes, body washes, and hand rubs, first aid antiseptics, health care personnel hand washes and hand rubs, surgical hand scrubs and rubs, and patient preoperative skin preparations. In 2013, FDA asked manufacturers to voluntarily revise the product labels for topical antiseptics to indicate whether the product is manufactured as a sterile or nonsterile product (Ref. 7).

Amendments of 1962, October 10, 1962, Pub. L. 87-781, Title I, sec. 101), and the first CGMP regulations followed in 1963 (*Part 133--Drugs; Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding*, 28 FR 6385 (June 20, 1963) available at: https://www.loc.gov/item/fr028120/). The regulations creating procedures for establishing OTC drug monographs were issued in 1972 (37 FR 9464 (May 11, 1972)) available at: https://www.loc.gov/item/fr037092/). Because of these subsequent statutes and regulations, § 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.

CGMP regulations require manufacturers to take steps to ensure that sterile drug products are free of objectionable microorganisms. (See, e.g., 21 CFR 211.28(a), 211.42(b) and (c), 211.67(a), 211.84(c), 211.110(a), 211.113(b), 211.165(b), 211.167(a).) The CGMP regulations also include provisions that ensure that irradiation or any other sterilization processes do not have a detrimental effect on a drug product's identity, strength, quality, purity, or stability. (See, e.g., 21 CFR 211.22, 211.25(b), 211.68, 211.100, 211.160(b), 211.165, 211.166.)

Numerous records relating to the manufacture of the drug product must be maintained and made available for inspection (21 CFR part 211, subpart J). FDA conducts inspections at manufacturing facilities, including irradiation facilities, to ensure that the CGMP regulations are followed. Inspection findings are reviewed and, when appropriate, action may be recommended against manufacturers observed to be out of compliance.

Choosing the sterilization process that is suitable for a particular drug product is the responsibility of the manufacturer and is an important part of pharmaceutical development. To

guide them in choosing an appropriate method of sterilization and otherwise complying with the CGMP requirements, manufacturers can turn to voluntary consensus standards that are widely-known by industry and recognized by FDA for the development, validation, and routine control of the sterilization of drugs by irradiation. As noted previously in this document, ISO publishes standards that address the different doses of radiation that are appropriate depending on the type and amount of microbiological contamination and the necessary degree of sterility assurance (Ref. 3). These include the following:

- ISO 11137-1:2006: Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices;
- ISO 11137-2:2013: Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose;
- ISO 11137-3:2006: Sterilization of health care products – Radiation – Part 3: Guidance on dosimetric aspects; and
- ISO/TS 13004:2013: Sterilization of health care products – Substantiation of selected sterilization dose: Method VDmaxSD.
- The USP also provides guidance on irradiation sterilization, including in chapter <1229.10>, which specifically addresses the topic (Ref. 3).

D. Conclusion

We propose the repeal of § 310.502(a)(11) because the Agency no longer concludes that drugs sterilized by irradiation are necessarily new drugs. The technology of controlled nuclear radiation for sterilization of drugs is now well understood and sterilization is a manufacturing

process that is adequately addressed by the regulations governing the OTC drug monograph system and CGMPs.

III. Legal Authority

FDA is issuing this proposed rule under the drugs and general administrative provisions of the FD&C Act (sections 201, 301, 501, 502, 503, 505, 510, 701, 702, and 704 (21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 371, 372, and 374)) and under section 361 of the Public Health Service Act (PHS Act) (42 U.S.C. 264). The FD&C Act gives us the authority to issue and enforce regulations designed to help ensure that drug products are safe, effective, and manufactured according to current good manufacturing practices, while section 361 of the PHS Act gives us the authority to issue and enforce regulations designed to prevent the introduction, transmission, or spread of communicable diseases.

IV. Proposed Effective Date

Any final rule that results from this proposed rule will be effective 30 days after the date of the final rule's publication in the *Federal Register*.

V. Economic Analysis of Impacts

We have examined the impacts of the proposed rule under 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.

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 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 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.

Table 1 summarizes our estimate of the annualized costs and benefits of the proposed 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	$0.00	$0.00	$0.00	2016	7%	10 years	Costs total less

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
	$millions/year							than $100
		$0.00	$0.00	$0.00	2016	3%	10 years	Costs total 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:			
Effects	State, Local or Tribal Government: None Small Business: None Wages: None Growth: None							

Because the proposed rule 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.--EO 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)

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.

VI. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) and 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Paperwork Reduction Act of 1995

This proposed rule refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information resulting from compliance with CGMPs have been approved under OMB control number 0910-0139.

VIII. Federalism

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

IX. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in EO 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the

Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

X. References

The following references are on display in 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. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. Jacobs, G., "Validation of the Radiation Sterilization of Pharmaceuticals." In: J. Agalloco and F. J. Carleton (eds.), *Validation of Pharmaceutical Processes* (3rd Ed.) Informa USA, New York, 2007.

2. Microbiology Sub-Committee, Radiation Sterilization Task Force, Parenteral Drug Association, Technical Report No. 11, "Sterilization of Parenterals by Gamma Radiation," *Journal of Parenteral Science and Technology*, 42 (3S), 1988, available at: https://store.pda.org/ProductCatalog/Product.aspx?ID=1170.

3. United States Pharmacopeial Convention (USP 40), Radiation Sterilization <1229.10>, 2017.

4. United States Pharmacopeial Convention (USP 40), Sterilization of Compendial Articles <1229>, 2017.

5. FDA Guidance for Industry on "Sterile Drug Products Produced by Aseptic Processing--Current Good Manufacturing Practice," September 2004; available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070342.pdf.

6. United States Pharmacopeial Convention (USP 40), Sterilization and Sterility Assurance of

Compendial Articles <1211>, 2017.

7. FDA Drug Safety Communication, "FDA Requests Label Changes and Single-Use Packaging for Some Over-the-Counter Topical Antiseptic Products to Decrease Risk of Infection," November 13, 2013; available at https://www.fda.gov/Drugs/DrugSafety/ucm374711.htm.

8. FDA Preliminary Regulatory Impact Analysis, Repeal of Regulation Requiring an Approved New Drug Application for Drugs Sterilized by Irradiation; https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.

List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 310 be amended as follows:

PART 310--NEW DRUGS

1. The authority citation for part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b-360f, 360j, 360hh-360ss, 361(a), 371, 374, 375, 379e, 379k-1; 42 U.S.C. 216, 241, 242(a), 262.

2. In § 310.502, revise paragraph (a) introductory text and remove and reserve paragraph (a)(11) to read as follows:

§ 310.502 Certain drugs accorded new drug status through rulemaking procedures.

(a) The drugs listed in this paragraph 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.

An approved new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act and part 314 of this chapter is required for marketing the following drugs:

* * * * *

(11) [Reserved]

* * * * *

Dated: September 7, 2018.

Scott Gottlieb,

Commissioner of Food and Drugs.

[FR Doc. 2018-19845 Filed: 9/11/2018 8:45 am; Publication Date: 9/12/2018]