



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 3

[Docket No. FDA-2004-N-0191]

Product Jurisdiction

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or Agency) is proposing to amend its regulations concerning the classification of products as biological products, devices, drugs, or combination products, and their assignment to Agency components for premarket review and regulation. This proposed rule would update the regulations to clarify the scope of the regulations, streamline and clarify the appeals process, align the regulations with more recent legislative and regulatory measures, update advisory content, and otherwise clarify the regulations, including updates to reflect Agency practices and policies. These changes are intended to enhance regulatory clarity and efficiency.

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-2004-N-0191 for “Product Jurisdiction.” 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: John Barlow Weiner, Associate Director for Policy, Office of Combination Products, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, Rm. 5129, Silver Spring, MD 20933, 301-796-8930, john.weiner@fda.hhs.gov.

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Executive Summary

FDA promulgated its product jurisdiction regulations, codified at part 3 (21 CFR part 3), in 1991 (see 56 FR 58754, November 21, 1991). Although FDA amended these regulations most recently in 2005, to clarify the meaning of the statutory term “primary mode of action” for assignment of combination products to Agency components (see 70 FR 49848, August 25, 2005), the regulations remain largely as published in 1991. However, relevant statutory provisions have changed; FDA has published additional policies so that the advisory content included in the regulations requires updating; and in other respects the rule warrants revisions to enhance clarity and efficiency. Accordingly, FDA is proposing to amend part 3 to: (1) clarify the scope of the regulations; (2) streamline and clarify the appeals process; (3) align the regulations with more recent legislative and regulatory measures; (4) update advisory content; and (5) otherwise clarify the rule, including updating it to reflect Agency policies and practices.

The incremental quantified cost savings of the proposed rule accrue to both the Agency and industry from resources, such as time and paper, saved through eliminating the part 3 appeal to the Office of Combination Products (OCP). These annual social cost savings are estimated to be \$28,000. Sponsors are expected to incur one-time costs to read and understand the regulation. Our primary estimate of the total cost to industry in the first year is approximately \$131,000.

The Agency estimates the quantifiable net social effect of the proposed rule to be a cost of approximately \$103,000 in the first year and a cost savings of approximately \$28,000 each year starting in the second year. The net present discounted value of the quantifiable net effect over 10 years is approximately \$114,000 at a 3 percent discount rate and \$76,000 at a 7 percent discount rate. The total annualized net effect of the proposed rule is estimated to produce an average net cost savings ranging from \$13,000 at a 3 percent discount rate and \$11,000 at a 7 percent discount rate.

I. Description of the Proposed Rule

For the reasons presented in the following subsections, FDA proposes to amend its regulations on Product Jurisdiction codified at part 3 to: (1) clarify the scope of the regulation; (2) streamline and clarify the appeals process; (3) align the regulations with more recent legislative and regulatory measures; (4) update advisory content; and (5) otherwise clarify the rule, including updating it to reflect Agency policies and practices.

A. *Clarify the Scope of the Regulation*

This proposed rule, if finalized, would amend § 3.3--Scope, to clarify that the part 3 procedures apply to sponsors (also referred to as applicants, see § 3.2--Definitions) for products for which the classification as biological products, devices, drugs, or combination products, or the Agency component with primary jurisdiction, is unclear or in dispute. It would also make conforming revisions to other sections in part 3, including the definitions in § 3.2.

FDA published its product jurisdiction regulations codified at part 3 in 1991, in part to implement section 503(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353(g)), which calls upon the Agency to assign products that are comprised of any combination of a drug and a device, a device and a biological product, a biological product and a drug, or a

drug, a device and a biological product (“combination products”) to Agency components based on the primary mode of action (PMOA) of the combination product. The rulemaking also established that the same procedures would be used to assign biological products, devices, and drugs to Agency components when their assignment was unclear or in dispute.

Although part 3 did not expressly refer to classification of products as biological products, devices, drugs, or combination products, such determinations are generally necessary to make an assignment determination. Non-combination products (biological products, devices, and drugs) are assigned to Agency components based on their classification. Accordingly, the Agency needs to determine, for example, whether a product is a biological product to be able to determine whether it should be assigned to a component that regulates biological products. Similarly, assignment of combination products is based on determining whether the product is a combination product and if so, which constituent part of the combination product (biological product, device, or drug) provides the PMOA (or applying the algorithm specified in § 3.4(b) if the PMOA cannot be determined with reasonable certainty).

Therefore, the Agency has been accepting under part 3 sponsor requests for the Agency to make product classification as well as assignment determinations (see, e.g., “How to Write a Request for Designation (RFD)”, at <https://www.fda.gov/regulatoryinformation/guidances/ucm126053.htm>). FDA’s longstanding acceptance and review of sponsors’ requests for product classification under part 3 is consistent with the obligations to which FDA became subject in 1998 under section 416 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105-115), which added section 563 to the FD&C Act (21 U.S.C. 360bbb-2). Section 563 of the FD&C Act requires FDA to classify products as biological products, devices, drugs, or combination products and to

assign products to an Agency component for regulation, in response to requests for designations submitted by product sponsors. The procedures at part 3 are appropriate for implementation of section 563 as well as section 503(g) of the FD&C Act, and FDA has used these procedures for both purposes to date.

This proposed rule would revise § 3.3 to clarify that FDA's procedures in part 3 apply to classification of products as biological products, devices, drugs, or combination products as well as to assignment of these products to Agency components, and would make corresponding amendments to other sections in part 3, including §§ 3.1, 3.7(c)(3) (see proposed 3.5(b)), 3.8(b) (see proposed 3.6(b)), 3.9(b) (see proposed 3.7(b)), and the definitions in § 3.2 for "letter of designation," "letter of request," and "product jurisdiction officer," to be consistent with this clarified statement of scope.

In addition, Agency experience over the 26 years since part 3 was codified has shown that sponsors sometimes are confused as to whether they must request a classification or assignment determination under part 3 as a prerequisite to making a premarket submission for their product, regardless of whether the classification or assignment for their product is unclear or in dispute. In addition, some entities who are not the sponsor for the product have attempted to obtain a product classification or assignment determination. To eliminate this confusion, this proposed rule would also revise § 3.3 to state that the part 3 procedures apply to sponsors if classification or assignment is unclear or in dispute for their product. If no such uncertainty exists, use of the procedures is unnecessary, and sponsors can engage directly with the appropriate Agency component. Further, clarifying that part 3 applies to sponsors is consistent with section 503(g) of the FD&C Act, as amended by the 21st Century Cures Act (Cures Act) (Pub. L. 114-255), and with section 563 of the FD&C Act.

B. Streamline and Clarify the Appeals Process for Product Classifications and Assignments

Section 3.8(c)--Requests for reconsideration. The proposed rule would remove, as confusing and inefficient, the process codified at § 3.8(c) for sponsors to request that the product jurisdiction officer reconsider determinations made under part 3.

Currently, a sponsor may make a request for reconsideration and if the sponsor disagrees with the decision upon reconsideration, the sponsor may make an additional, supervisory appeal in accordance with § 10.75 (21 CFR 10.75). Alternatively, the sponsor may directly submit such a supervisory appeal without first requesting reconsideration under § 3.8(c).

This current approach has proven confusing to sponsors and inefficient for sponsors and Agency staff. Determinations under part 3 are made through a robust process involving OCP's review of information, either provided by the sponsor or otherwise available to the Agency, in consultation with regulatory, legal, and scientific staff from other Agency components, as appropriate. Consistent with appeals under § 10.75, no new information may be presented in a request for reconsideration under § 3.8(c). Because determinations under part 3 are made through a robust process, further evaluation of the same data and information by OCP is unlikely to result in a change of decision. Requests for reconsideration have been inefficient for sponsors who have opted to utilize this mechanism, and inclusion of the request for reconsideration mechanism has led to confusion, with sponsors sometimes believing they must make a request for reconsideration before they may submit a § 10.75 supervisory appeal.

Accordingly, FDA has determined that the request for reconsideration process is unhelpful to retain.

C. Aligning Part 3 with More Recent Legislative and Regulatory Measures

In addition to the amendments made by section 416 of FDAMA regarding classification and assignment discussed in section I.A, two other statutory changes have been made relating to issues addressed in part 3 since FDA promulgated the part 3 regulations in 1991, and this rule proposes to amend part 3 to comport with these statutory changes as well.

FDA amended part 3 in 2005 to clarify the meaning of PMOA for assignment of combination products, and to codify at § 3.2 definitions for biological product, device, and drug “modes of action” based upon the statutory definitions of biological product, device, and drug. The Biologics Price Competition and Innovation Act of 2009 (Subtitle A of Title VII of the Patient Protection and Affordable Care Act (Pub. L. 111-148)) amended the definition for biological product at section 351(i) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(i)) to address expressly and more precisely the classification of proteins as biological products. This proposed rule would amend the definition for “biological product mode of action” at § 3.2 to align with the current statutory definition for biological product.

In 2016, section 3038 of the Cures Act amended section 503(g) of the FD&C Act, to include additional provisions relating to intercenter consultation and coordination (see 21 U.S.C. 353(g)(8)(C)), reinforcing expectations that intercenter consultation and coordination occur as appropriate. Currently, § 3.4(c) states in part that the designation of a center (an “agency component” as defined in § 3.2) as having primary jurisdiction for a combination product does not preclude consultations by that component with other components. In keeping with section 503(g) of the FD&C Act as amended and Agency practice, the Agency is revising § 3.4(c) to make clear that consultations with other Agency components will occur as FDA deems appropriate. Agency practice is to conduct intercenter consultation and coordination routinely to

ensure appropriate expertise is brought to bear to enable fully informed reviews and consistent regulation of products.

In addition, section 503(g) of the FD&C Act, as amended by section 3038 of the Cures Act, states that combination products shall be reviewed under a single application whenever appropriate, and that sponsors may submit separate applications for the constituent parts of a combination product unless FDA determines a single application is necessary (see 21 U.S.C. 353(g)(1)(B) and (6)). Currently, § 3.4(c) states in part that the Agency can require in appropriate cases that constituent parts of a combination product be reviewed under separate applications. Accordingly, to avoid confusion that might arise from maintaining this different articulation of Agency authority on this topic, the proposed rule would remove this language at § 3.4(c). FDA intends to issue guidance regarding implementation of the new statutory provisions as needed given Agency experience with implementing them.¹

The rule uses the term “application,” and lists types of applications within the definition for “premarket review” at § 3.2. However, the types of premarket submissions for medical products have changed since publication of part 3, and this listing is now incomplete. To enhance clarity and completeness, the proposed rule would add a current, complete definition for “application,” and remove the existing, related language currently included in the definition for “premarket review” in § 3.2. In addition, for clarity and alignment with Agency practice, the

¹ Section 3038 of the Cures Act also amended section 503(g) of the FD&C Act in other respects relating to combination product assignment, including to: incorporate a definition for PMOA, which is consistent with the regulatory definition of PMOA at § 3.2, promulgated by FDA in its 2005 amendments to part 3 (see 21 U.S.C. 353(g)(1)(C)); provide that drug or biological product PMOA cannot be based solely upon the product having any chemical action within or on the human body (see 21 U.S.C. 353(g)(1)(E)); provide that sponsors who disagree with FDA’s PMOA determination may request a substantive rationale of the determination (see 21 U.S.C. 353(g)(1)(F)(i)); and provide a mechanism for sponsors and FDA to collaborate and seek agreement on studies to establish the relevance of the chemical action in achieving the PMOA of their products if they do not agree with the Agency’s PMOA determination (see 21 U.S.C. 353(g)(1)(F)(ii)). These amendments serve to codify longstanding Agency regulatory interpretations and practices. Accordingly, FDA has determined that revision of part 3 with respect to these statutory amendments is not necessary.

proposed rule would revise § 3.2 to define premarket review to include examination of data and information “submitted by an applicant,” rather than “in an application,” since premarket review can include Agency review of information provided as part of “pre-submission” engagement with applicants.

In addition, the proposed rule would amend § 3.2--Definitions to include a cross-reference to the definition for “constituent part,” codified at 21 CFR 4.2 in the 2013 rulemaking regarding current good manufacturing practices for combination products, and which has also been referenced at 21 CFR 4.101 as part of the 2016 rule on postmarketing safety reporting for combination products (81 FR 92603). The meaning of the term is the same for purposes of part 3 as for purposes of part 4. Accordingly, cross-referencing the definition into part 3 would serve to ensure clarity and consistency.

D. Update Advisory Content

Part 3 includes advisory language and addresses associated with Agency guidance in various locations. As a general matter, recommendations from FDA are provided in guidance documents published in accordance with good guidance practices (see 21 CFR 10.115). This approach not only enables the public to comment on proposed guidance, but also enables FDA to update guidance in a timely manner given stakeholder and Agency experience with the policy topic. FDA included advisory content in part 3 in light of the novelty of the regulatory topic at the time, to facilitate stakeholder understanding and indicate Agency thinking. However, Agency thinking has evolved since promulgation of part 3 and more complete, current guidance documents and other policy statements are now available. Accordingly, the proposed rule, if finalized, would remove the advisory content and discussion of guidance from part 3.

Specifically, this proposed rule would remove the provisions at §§ 3.2, 3.5, and 3.7, as explained below.

Section 3.2 includes in the definition for “mode of action” a reference to constituent parts of combination products each providing one type of mode of action and notes that the mode of action of each constituent part is typically identifiable. The proposed rule would replace this potentially confusing language, with a simple statement that each constituent part contributes one mode of action (device, drug, or biological product). Modes of action of a combination product and how to address them in requests for assignment are more fully addressed in Agency guidance, including in “How to Write a Request for Designation (RFD).”

Section 3.5 addresses the relationship between part 3 and intercenter agreements on product assignment. The proposed rule would remove this section. These non-binding intercenter agreements adopted in 1991 address the assignment of biological products, devices, and drugs, as well as combination products. The Medical Device User Fee and Modernization Act (MDUFMA) (Pub. L. 107-250) enacted in 2002 amended section 503(g) of the FD&C Act to require FDA to review each agreement, guidance, or practice addressing the assignment of combination products to Agency centers, for consistency with section 503(g) (see 21 U.S.C. 353(g)(8)(F)). In accordance with this mandate, FDA conducted a review, including of the intercenter agreements addressed in § 3.5, and published its assessment in 2006 (see “Jurisdictional Update: Intercenter Agreements”, at <https://www.fda.gov/CombinationProducts/JurisdictionalInformation/JurisdictionalUpdates/ucm106506.htm>). The Agency concluded that: (1) the usefulness of these agreements was becoming increasingly limited; (2) that they should not be relied upon independently as the most current, accurate jurisdictional statements; and (3) that issuance of new guidance and other efforts should

be pursued to enhance transparency and more clearly articulate the principles upon which jurisdictional determinations are based. Consistent with that assessment, FDA has since published various policy statements relating to product classification and assignment and posted various other relevant materials on its website (see <https://www.fda.gov/CombinationProducts/default.htm>), most recently, a final guidance on “Classification of Products as Drugs and Devices and Additional Product Classification Issues” (September 2017) (<https://www.fda.gov/RegulatoryInformation/Guidances/ucm258946.htm>). The Agency is currently reviewing these intercenter agreements to determine what action, if any, to take with respect to them.

Sections 3.7(a) and (b) include recommendations regarding who should file an RFD and when they should file them, respectively. The proposed rule, if finalized, would remove these provisions. These questions are addressed by the proposed amendments to § 3.3 discussed in section I.A, and current Agency guidance, including in “How to Write a Request for Designation (RFD)”, which provides more clear and complete recommendations regarding timing and other process considerations.

E. Other Clarifications to the Rule

Section 3.2 defines mode of action, and what constitutes a biological product, device, and drug mode of action, for purposes of making combination product assignment determinations. To enhance clarity, the proposed rule would add an express statement that the mode of action definitions apply for purposes of making combination product assignment determinations, and would simplify the definition for device mode of action at § 3.2 by referring to the statutory definition of device provided in section 201(h) of the FD&C Act (21 U.S.C. 321(h)) and removing redundant language.

Section 3.4(a)--Designated Agency component. The proposed rule would amend § 3.4(a) to clarify that the Agency component to which a combination product is assigned based on PMOA is the component that regulates the constituent part providing the PMOA. For example, some biological products are assigned to the Center for Biologics Evaluation and Research (CBER) and others are assigned to the Center for Drug Evaluation and Research (CDER). If a combination product has a biological product PMOA, it is assigned to either CBER or CDER based upon which of these two Centers regulate that type of biological product. This interpretation of the statutory provisions governing PMOA and combination product assignments is consistent with Agency practice and ensures that combination products are assigned to the Agency component most familiar with the constituent part that provides the PMOA.

Sections 3.2 and 3.6--Product jurisdiction officer. Section 3.2 includes a definition of “product jurisdiction officer” and section 3.6 specifies that OCP is the designated product jurisdiction officer. The proposed rule would revise the definition for “product jurisdiction officer” at § 3.2 to include information currently provided in § 3.6, and remove § 3.6, simplifying the rule by consolidating this related information. Specifically, the definition of “product jurisdiction officer” at § 3.2 would be revised to refer to OCP as the office responsible for classification and assignment of medical products. MDUFMA required FDA to establish an office to perform various regulatory functions relating to combination products, including their assignment to Agency components. Consistent with that mandate, FDA created OCP and delegated to specified staff within OCP the authority to classify products as biological products, devices, drugs, or combination products as well as to assign these products to an Agency component with primary jurisdiction for their premarket review and regulation.

Existing section 3.7(d) addresses where to file RFD communications and currently requires submission in hard copy with the option to submit electronically as well. FDA sees no reason to continue to require a hard copy submission and proposes to revise the provision (see proposed § 3.5(b)) and make corresponding revisions to the content of § 3.7(c) (see proposed 3.5(b)) to give sponsors the alternative of submitting solely electronically. In addition, to avoid the need to revise the rule given changes to OCP's mailing address or email address, this rule would amend § 3.7(d) (see proposed 3.5(b)) to direct sponsors to submit RFDs to the current mailing address or email address for OCP as published by FDA, currently on the Office of Combination Products webpage (<https://www.fda.gov/CombinationProducts/default.htm>).

Section 3.9(b) addresses grounds for changing a classification or assignment designation, including circumstances under which the Agency can do so without the consent of the sponsor. It currently provides that sponsors shall be given 30 days written notice (which can be via email) of proposed changes and that such changes require the concurrence of the Principal Associate Commissioner. Because positions and titles in the Agency change from time to time, to avoid the need to revise part 3 when such changes occur, this rule would revise § 3.9(b) (see proposed § 3.7(b)) to state that such changes of classification or assignment require the concurrence of the official in the Agency responsible for the oversight of OCP.

Other clarifying changes to part 3 include in § 3.2: in the definitions of "combination product" and "product," changing "biologic" to "biological product" to provide for consistency in part 3 and with the term used in section 351 of the PHS Act; and in the definitions of "biological product" and "product," changing "351(a)" to "351(i)" and "262(a)" to "262(i)" so that the correct provision in the PHS Act and the U.S. Code is cited (i.e., the provision that defines "biological product").

II. Legal Authority

The Agency derives its authority to issue the regulations found in part 3 from 21 U.S.C. 321, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 360gg-360ss, 360bbb-2, 371(a), 379e, 381, 394; 42 U.S.C. 216, 262, and 264. Congress expressly directed FDA to assign combination products to the appropriate Agency component for regulation based on the Agency's assessment of PMOA as set forth in section 503(g) of the FD&C Act. Congress also expressly directed FDA to determine the classification of a product as a drug, biological product, device, or combination product, or the component of the Agency that will regulate the product, as applicable, in response to a request submitted under section 563 of the FD&C Act. Under section 701 of the FD&C Act (21 U.S.C. 371) and for the efficient enforcement of the FD&C Act, FDA has the authority to issue and amend the regulations found in part 3.

III. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no new collection of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 is not required. Information collection under part 3 has already been approved under OMB control number 0910-0523.

IV. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) 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.

V. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the 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 Executive order and, consequently, a federalism summary impact statement is not required.

VI. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 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.

VII. Preliminary Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the proposed 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 proposed 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 this rule imposes no new burdens, 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 threshold after adjustment for inflation is \$148 million, using the most current (2016) 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

The objective of this proposed rule is to amend the regulations concerning RFDs of the classification of products as biological products, devices, drugs, or combination products, or their assignment to Agency components for premarket review and regulation. The proposed rule is intended to clarify the scope of the regulations, streamline and clarify the appeals process, align the regulations with more recent legislative and regulatory measures, update advisory content, and otherwise to clarify part 3.

Many provisions of this proposed rule codify current practices and may not result in estimated costs, benefits, or savings. However, we expect a few provisions to lead to changes

that may generate additional public health benefits and cost savings to society. A summary of the quantified costs and cost savings of the proposed rule are presented in table 1. The lower and upper estimates given in table 1 are at the 5 and 95 percent interval, respectively.

Table 1.--Summary of Net Cost Savings of the Proposed Rule^{1,2}

Category	Primary Estimate	Low Estimate	High Estimate
Costs	Annualized Monetized \$/year	\$17,000	\$12,000
	Annualized Quantified		
	Qualitative		

¹ We use a 10-year time horizon for this rule with payments occurring at the end of each period.

² All dollar values are rounded to the nearest \$1,000.

The estimated primary costs of the proposed rule include the additional one-time costs incurred by industry to read and understand the regulation. We expect only a subset of firms currently producing medical products will incur this cost. Our primary estimate of the total up-front cost to industry is approximately \$131,000. Annualizing these costs over a 10-year period, we estimate total annualized costs to be \$15,000 at a 3 percent discount rate, and \$17,000 at a 7 percent discount rate. The present value of these costs over 10 years is \$127,000 at a 3 percent discount rate, and \$122,000 at a 7 percent discount rate.

The primary public health benefit from adoption of the proposed rule would be the value of the illnesses and deaths avoided as a result of finalizing the proposed rule. Current regulatory requirements may cause applicants to unnecessarily submit RFDs, or to make misguided judgments regarding the need to confirm product classification or assignment. The reduction in uncertainty about the RFD process will, thereby, potentially allow sponsors to make more informed decisions regarding product development and seeking marketing authorization, and potentially allow sponsors and FDA personnel to divert resources used under current regulations to other areas, such as to product development and marketing applications. We are not able to quantify or to identify specific ways by which the proposed rule would lead to avoided illnesses or deaths and therefore do not include public health benefits in our net estimates.

FDA is able to quantify the resource savings to both the Agency and industry from the proposed rule associated with streamlining and clarifying the appeals process for product classification and assignments. Our primary estimate of total cost savings to industry and FDA is approximately \$28,000 annually. The present value of these savings over 10 years is \$241,000 at a 3 percent discount rate, and \$198,000 at a 7 percent discount rate. Potential resource savings to FDA and industry from the optional electronic submission of RFDs are not included in this estimate because of the uncertainty in the number of sponsors who would choose to submit electronically.

Our best estimate of the quantifiable net social effect of the proposed rule, using a 10-year time horizon, is a cost of approximately \$103,000 in the first year and a cost savings of approximately \$28,000 each year starting in the second year. The net present discounted value of the quantifiable cost savings over 10 years is approximately \$114,000 at a 3 percent discount rate and approximately \$76,000 at a 7 percent discount rate. The total annualized net effect of the proposed rule is estimated to produce an average net cost savings ranging from \$13,000 at a 3 percent discount rate and \$11,000 at a 7 percent discount rate.

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 the proposed rule, if finalized, is not significant under Executive Order 12666 and is deregulatory under Executive Order 13771.

The present value of our primary net cost savings estimate of the proposed rule, using an infinite time horizon, is approximately \$281,000, discounted at 7 percent, with a lower bound of approximately \$165,000 and an upper bound of approximately \$1.2 million. The annualized net cost savings of the proposed rule are approximately \$20,000, discounted at 7 percent on an

infinite time horizon, with a lower bound of approximately \$12,000 and an upper bound of approximately \$83,000. Discounted at 3 percent, the present value of our primary net cost savings of the proposed rule is approximately \$814,000, with a lower bound of approximately \$634,000 and an upper bound of approximately \$2.9 million. The annualized net cost of the proposed rule is approximately -\$20,000, discounted at 3 percent on an infinite time horizon, with a lower bound of approximately -\$12,000 and an upper bound of approximately -\$83,000. The estimated net costs using a 7 percent discount rate under Executive Order 13771 are summarized in table 2.

Table 2.--Summary of Executive Order 13771 Net Costs of the Proposed Rule^{1,2,3}

	Primary (7%)	Lower Bound (7%)	Upper Bound (7%)
Present Value of Costs	\$122,000	\$81,000	\$192,000
Present Value of Savings	\$403,000	\$357,000	\$1,266,000
Present Value of Net Costs	\$281,000	\$165,000	\$1,184,000
Annualized Costs	\$9,000	\$6,000	\$13,000
Annualized Savings	\$28,000	\$25,000	\$89,000
Annualized Net Costs	-\$20,000	-\$12,000	-\$83,000

¹ We use an infinite time horizon for this rule with payments occurring at the end of each period.

² All dollar values are rounded to the nearest \$1,000.

³ A negative net cost implies a net cost savings.

The Regulatory Flexibility Act requires Agencies to prepare an initial regulatory flexibility analysis if a proposed rule would have a significant economic impact on a substantial number of small entities (including small businesses, small non-profit organizations, and small governmental jurisdictions). FDA has examined the economic implications of the proposed rule as required by the Regulatory Flexibility Act. This rule, if finalized, will not impose any new burdens on small entities, and thus will not have a significant economic impact on a substantial number of small entities.

The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 1) and at <https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

VIII. Proposed Effective Date

FDA is proposing that any final rule based on this proposed rule become effective 30 days after the date of its publication in the *Federal Register*.

IX. Reference

The following reference is on display in the Dockets Management Staff (see ADDRESSES) and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it is also available electronically at <https://www.regulations.gov> or <https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

1. Preliminary Regulatory Impact Analysis of the Proposed Rule, Amendments to 21 CFR Part 3--Product Jurisdiction, Docket No. FDA-2004-N-0191.

List of Subjects in 21 CFR Part 3

Administrative practice and procedure, Biological products, Combination products, Drugs, Medical devices, Authority delegations.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 3 be amended as follows:

1. The authority citation for part 3 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 360gg-360ss, 360bbb-2, 371(a), 379e, 381, 394; 42 U.S.C. 216, 262, 264.

2. Revise part 3 to read as follows:

PART 3--PRODUCT JURISDICTION

Subpart A--Product Classification and Assignment of Agency Component for Review of

Premarket Applications

Sec.

3.1 Purpose.

3.2 Definitions.

3.3 Scope.

3.4 Designated agency component.

3.5 Request for designation.

3.6 Letter of designation.

3.7 Effect of letter of designation.

3.8 Stay of review time.

Subpart B [Reserved]

§ 3.1 Purpose.

The purpose of this subpart is to provide procedures for determining whether a product is a biological product, device, drug, or combination product, and which component within FDA will have primary jurisdiction for a biological product, device, drug, or combination product, where product classification or assignment is unclear or in dispute. By doing so, this subpart implements section 503(g) of the Federal Food, Drug, and Cosmetic Act. Nothing in this subpart prevents FDA from using any agency resources it deems necessary to ensure adequate review of the safety and effectiveness of any product, or the substantial equivalence of any device to a predicate device.

§ 3.2 Definitions.

For the purpose of this part:

Agency means the Food and Drug Administration.

Agency component means the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Center for Drug Evaluation and Research, or alternative organizational component of the agency.

Applicant means any person who submits or plans to submit an application to the Food and Drug Administration for premarket review. For purposes of this section, the terms “sponsor” and “applicant” have the same meaning.

Application means any investigational new drug application, investigational device exemption application, new drug application, abbreviated new drug application, biologics license application, premarket notification submission, De Novo classification request, premarket approval application, product development protocol, or humanitarian device exemption application, including all amendments and supplements.

Biological product has the meaning given the term in section 351(i) of the Public Health Service Act (42 U.S.C. 262(i)).

Combination product includes:

(1) A product comprised of two or more regulated components, i.e., drug/device, biological product/device, drug/biological product, or drug/device/biological product, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

(2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

(3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

(4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Constituent part has the meaning given the term in § 4.2 of this chapter.

Device has the meaning given the term in section 201(h) of the Federal Food, Drug, and Cosmetic Act.

Drug has the meaning given the term in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act.

FDA means Food and Drug Administration.

Letter of designation means the written notice issued by the product jurisdiction officer classifying the product, specifying the agency component with primary jurisdiction, or both.

Letter of request means an applicant's written submission to the product jurisdiction officer seeking product classification, the designation of the agency component with primary jurisdiction, or both.

Mode of action is the means by which a product achieves an intended therapeutic effect or action. For purposes of this definition, "therapeutic" action or effect includes any effect or

action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body. When making assignments of combination products under this part, the agency will consider three types of mode of action: the actions provided by a biological product, a device, and a drug. Each constituent part of a combination product has one such type of mode of action. For purposes of combination product assignment:

(1) A constituent part has a biological product mode of action if it acts by means of a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings, as described in section 351(i) of the Public Health Service Act.

(2) A constituent part has a device mode of action if it meets the definition of device contained in section 201(h) of the Federal Food, Drug, and Cosmetic Act, and it does not have a biological product mode of action.

(3) A constituent part has a drug mode of action if it meets the definition of drug contained in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act, and it does not have a biological product or device mode of action.

Premarket review includes the examination of data and information submitted by an applicant.

Primary mode of action is the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.

Product means any article that contains any drug as defined in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act; any device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act; or any biological product as defined in section 351(i) of the Public Health Service Act (42 U.S.C. 262(i)).

Product jurisdiction officer is the person or persons in the Office of Combination Products responsible for classification of products as biological products, devices, drugs, and combination products and for designating the component of FDA with primary jurisdiction for the premarket review and regulation of such products.

Sponsor means “applicant” as defined in this section.

§ 3.3 Scope.

This subpart applies to sponsors for products for which classification as a drug, device, biological product, or combination product, or the agency component with primary jurisdiction, is unclear or in dispute.

§ 3.4 Designated agency component.

(a) To designate the agency component with primary jurisdiction for the premarket review and regulation of a combination product, the agency shall determine the primary mode of action of the product. Where the primary mode of action is that of:

(1) A drug (other than a biological product), the agency component charged with premarket review of such drugs shall have primary jurisdiction;

(2) A device, the agency component charged with premarket review of such devices shall have primary jurisdiction;

(3) A biological product, the agency component charged with premarket review of such biological products shall have primary jurisdiction.

(b) In some situations, it is not possible to determine, with reasonable certainty, which one mode of action will provide a greater contribution than any other mode of action to the overall therapeutic effects of the combination product. In such a case, the agency will assign the combination product to the agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole. When there are no other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole, the agency will assign the combination product to the agency component with the most expertise related to the most significant safety and effectiveness questions presented by the combination product.

(c) The agency component with primary jurisdiction for the premarket review and regulation of a product will consult with other agency components, as FDA deems appropriate.

§ 3.5 Request for designation.

(a) What to file: a request for designation may be submitted only by the sponsor and must be filed in accordance with this section. The request for designation must not exceed 15 pages, including attachments, and must set forth:

(1) The identity of the sponsor, including company name and address, establishment registration number, company contact person, email address, and telephone number.

(2) A description of the product, including:

(i) Classification, name of the product and all component products, if applicable;

(ii) Common, generic, or usual name of the product and all component products;

(iii) Proprietary name of the product;

(iv) Identification of any component of the product that already has received premarket approval, is marketed as not being subject to premarket approval, or has received an

investigational exemption, the identity of the sponsors, and the status of any discussions or agreements between the sponsors regarding the use of this product as a component of a new combination product.

(v) Chemical, physical, or biological composition;

(vi) Status and brief reports of the results of developmental work, including animal testing;

(vii) Description of the manufacturing processes, including the sources of all components;

(viii) Proposed use or indications;

(ix) Description of all known modes of action, the sponsor's identification of the single mode of action that provides the most important therapeutic action of the product, and the basis for that determination;

(x) Schedule and duration of use;

(xi) Dose and route of administration of drug or biological product;

(xii) Description of related products, including the regulatory status of those related products; and

(xiii) Any other relevant information.

(3) The sponsor's recommendation as to the classification of the product as a drug, device, biological product, or combination product, or as to which agency component should have primary jurisdiction. For combination products, the recommendation for primary jurisdiction must be based on the primary mode of action unless the sponsor cannot determine with reasonable certainty which mode of action provides the most important therapeutic action of the combination product, in which case the sponsor's recommendation must be based on the

assignment algorithm set forth in § 3.4(b) and an assessment of the assignment of other combination products the sponsor wishes FDA to consider during the assignment of its combination product.

(b) How and where to file: all communications pursuant to this subpart shall be addressed to the attention of the product jurisdiction officer and plainly marked “Request for Designation.” Such communications shall be submitted either in hard copy (an original and two copies) or in an electronic format that FDA can process, review, and archive, to the current mailing address or email address, respectively, for the Office of Combination Products as published by FDA.

§ 3.6 Letter of designation.

(a) Each request for designation will be reviewed for completeness within 5 working days of receipt. Any request for designation determined to be incomplete will be returned to the applicant with a request for the missing information. The sponsor of an accepted request for designation will be notified of the filing date.

(b) Within 60 days of the filing date of a request for designation, the product jurisdiction officer will issue a letter of designation to the sponsor, with copies to the agency components, specifying the classification of the product at issue or the agency component designated to have primary jurisdiction for the premarket review and regulation of the product at issue, and any consulting agency components. The product jurisdiction officer may request a meeting with the sponsor during the review period to discuss the request for designation. If the product jurisdiction officer has not issued a letter of designation within 60 days of the filing date of a request for designation, the sponsor’s recommendation of the classification of the product or the

center with primary jurisdiction, in accordance with § 3.5(a)(3), shall become the designated product classification or agency component.

§ 3.7 Effect of letter of designation.

(a) The letter of designation constitutes an agency determination that is subject to change only as provided in paragraph (b) of this section.

(b) The product jurisdiction officer may change the designated product classification or agency component with the written consent of the sponsor, or without its consent to protect the public health or for other compelling reasons. A sponsor shall be given 30 days written notice of any proposed such change in designated product classification or agency component. The sponsor may request an additional 30 days to submit written objections, not to exceed 15 pages, to the proposed change, and shall be granted, upon request, a timely meeting with the product jurisdiction officer and appropriate center officials. Within 30 days of receipt of the sponsor's written objections, the product jurisdiction officer shall issue to the sponsor, with copies to appropriate agency component officials, a written determination setting forth a statement of reasons for the proposed change in designated product classification or agency component. Such a change in the designated product classification or agency component requires the concurrence of the official in the agency responsible for overseeing the Office of Combination Products.

§ 3.8 Stay of review time.

Any filing with or review by the product jurisdiction officer stays the review clock or other established time periods for agency action for an application during the pendency of the review by the product jurisdiction officer.

Subpart B [Reserved]

Dated: May 10, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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