Preliminary Economic Analysis of Impacts Of Intended Uses Proposed Rule

A. Introduction and Summary

1. 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." This proposed rule is not expected to be subject to the requirements of EO 13771 because this proposed rule is expected to result in no more than *de minimis* costs. This proposed rule is 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. We cannot predict how many companies may revise labeling, advertising, or other materials, or otherwise modify their behavior, following issuance of this rule. However, because this rule would merely clarify, but not change, the types of evidence relevant to determining manufacturers' intended use of products, any such changes would be voluntarily undertaken by firms. Because the proposed rule would not extend FDA's authority to additional products or impose any additional requirements on currently regulated products, we expect the proposed rule will impose negligible

costs, if any. As a result, 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 $154 million, using the most current (2018) 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.

2. Summary of Costs and Benefits

The proposed rule clarifies but does not change FDA's interpretation and application of existing intended use regulations for medical products.

The benefits of this rule are additional clarity and certainty for manufacturers and stakeholders regarding evidence that is relevant in evaluating whether an article is intended for use as a drug or device.

This proposed rule is not expected to impose any significant additional costs on firms. Although this rule may impact firms' future marketing, product development, and communication strategies, firms are not required to make any changes to labeling, marketing materials, or operating procedures. Additionally, this rule does not extend FDA's jurisdiction to any new products.

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

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits						7%		

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
	Annualized Monetized $millions/year					3%		
	Annualized Quantified					7%		
						3%		
	Qualitative	Clarification of intended use interpretation and application						
Costs	Annualized Monetized $millions/year					7%		
						3%		
	Annualized Quantified					7%		
						3%		
	Qualitative	Negligible costs, if any						
Transfers	Federal Annualized Monetized $millions/year					7%		
						3%		
	From/ To	From:			To:			
	Other Annualized Monetized $millions/year					7%		
						3%		
	From/To	From:			To:			
Effects	State, Local or Tribal Government: None Small Business: None Wages: None Growth: None							

B. Preliminary Economic Analysis of Impacts

1. Background

This rule clarifies FDA's longstanding position that the intended use of a drug or device product can be based on any relevant source of evidence by describing types of evidence relevant to the intended use of a product and types of evidence that, standing alone, are not determinative of intended use.

One important clarification involves a manufacturer's knowledge of unapproved uses of its approved product. Current versions of §§ 201.128 and 801.4 specify that a manufacturer of a drug (§201.128) or device (§801.4) must include adequate labeling if it knows its product is used

for an unapproved purpose. The September 2015 proposed rule (80 FR 57756 at 57764) removed the sentence regarding the requirement to provide adequate labeling if a firm knows its product is being used for an unapproved use. The amended January 2017 final rule (82 FR 2193 at 2217) was intended to clarify FDA's position by requiring manufacturers to include adequate labeling "if the totality of the evidence establishes that a manufacturer objectively intends that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than ones for which it is approved (if any)."

In the *Federal Register* of February 7, 2017 (82 FR 9501), FDA delayed the effective date of the January 2017 final rule until March 2017. In February 2017, various industry organizations filed a petition raising concerns with the January 2017 final rule, requesting reconsideration and a stay. The petition requested that FDA reconsider the amendments to the "intended use" regulations and issue a new final rule that, with respect to the intended use regulations at §§ 201.128 and 801.4, reverted to the language of the September 2015 proposed rule. The petition also requested that FDA indefinitely stay the rule because petitioners argued that the final rule was issued in violation of the fair notice requirement under the Administrative Procedure Act and that the "totality of the evidence" language in the 2017 final rule was a new and unsupported legal standard.

In the *Federal Register* of March 20, 2017 (82 FR 14319), FDA further delayed the effective date of the final rule until March 2018 and opened the docket for additional public comment. Following some comments supporting the delay and proposing specific changes to the language in §§ 201.128 and 801.4, on March 16, 2018 (83 FR 11639), FDA delayed the amendments to §§ 201.128 and 801.4 until further notice. This proposed rule adopts the general approach set forth in the September 2015 proposed rule by deleting the final sentence; the

proposed rule also clarifies FDA's interpretation and application of evidence relevant to determining intended use.

2. Benefits of the Proposed Rule

The proposed rule clarifies FDA's existing interpretation of the determination of the intended use of drugs and devices. This clarification should reduce manufacturer and stakeholder uncertainty regarding the scenarios in which specific types of evidence may or may not show a product is intended for a drug or device use. Removal of the final sentence in §§ 201.128 and 801.4 and the inclusion of a new clarifying clause ("provided, however, that a firm would not be regarded as intending an unapproved new use for an [approved or cleared medical product] based solely on that firm's knowledge that such [product] was being prescribed or used by health care providers for such use") eliminate any question about whether manufacturers need to think about developing an action plan or strategy related to a potential new intended use of their approved or cleared medical products due merely to knowledge of unapproved uses of these products by third parties. We believe this clarification is the benefit of the proposed rule; we request comment on this assumption.

3. Costs of the Proposed Rule

The proposed rule is not expected to impose significant additional costs on manufacturers and distributors of FDA-regulated products. The proposed rule does not extend FDA's regulatory authority to any new or additional products, nor does the rule change the current approach to evaluating intended use or impose any additional requirements on manufacturers or distributors. We do not have any reason to believe firms will change their marketing or operating procedures as a result of this rule. We request comment on this assumption. We do not have evidence that this proposed rule would impose costs on currently marketed products. We

request comment on this assumption.

C. Initial Small Entity Analysis

In Table 2, we describe the Small Business Administration's size thresholds for industries affected by the proposed rule. Based on US Census data, at least 22.9% of businesses in NAICS code 21323 (Tobacco Manufacturing) are considered small; at least 17.5% of businesses in NAICS code 32541 (Pharmaceutical and Medicine Manufacturing) are considered small; and at least 32.6% of businesses in NAICS code 33911 (Medical Equipment and Supplies Manufacturing) are considered small. Because the proposed rule is not expected to impose costs on manufacturers or distributors of FDA-regulated products, the proposed rule is also not expected to impose costs on small entities. Therefore, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

Table 2: Small Business Administration Size Standards for Affected Industries

NAICS Code	Industry Description	Small Business Threshold
312230	Tobacco Manufacturing	Fewer than 1,500 Employees
325411	Medicinal and Botanical Manufacturing	Fewer than 1,000 Employees
325412	Pharmaceutical Preparation Manufacturing	Fewer than 1,250 Employees
325413	In-vitro Diagnostic Substance Manufacturing	Fewer than 1,250 Employees
325414	Biological Product (except Diagnostic) Manufacturing	Fewer than 1,250 Employees
339112	Surgical and Medical Instrument Manufacturing	Fewer than 1,000 Employees
339113	Surgical Appliance and Supplies Manufacturing	Fewer than 750 Employees

339114	Dental Equipment and Supplies Manufacturing	Fewer than 750 Employees
339115	Ophthalmic Goods Manufacturing	Fewer than 1,000 Employees
339116	Dental Laboratories	Fewer than 500 Employees

XII. References

The following references marked with an asterisk (*) 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. References without asterisks are not on public display at https://www.regulations.gov because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. 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. Plaintiff's Memorandum of Law at 38-40, *Allergan Inc.* v. *United States*, 1:09-cv-01879-JDB (D.D.C. January 15, 2010).

*2. Complaint at ¶¶ 35-37, *Par Pharmaceutical Inc.* v. *United States*, 1:11-cv-01820 (D.D.C. October 10, 2011).

*3. Citizen Petition from the Medical Information Working Group at 18, FDA-2013-P-1079 (Sept. 3, 2013).

*4. Memorandum for the Heads of Executive Departments and Agencies, from Reince Priebus, Assistant to the President and Chief of Staff, "Regulatory Freeze Pending Review," January 20, 2017 (available at https://www.whitehouse.gov/presidential-actions/memorandum-heads-executive-departments-agencies/), accessed February 5, 2020.

5. Zettler, P.J., N. Hemmerich, and M.L. Berman, "Closing the Regulatory Gap for Synthetic Nicotine Products," *Boston College Law Review*, vol. 59(6), pp. 1933-1982, 1970 (published online 2018) (available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6329380/), accessed February 5, 2020.

*6. FDA, Guidance for Industry, "Medical Product Communications That Are Consistent With the FDA-Required Labeling--Questions and Answers," June 2018 (available at https://www.fda.gov/media/102575/download), accessed February 5, 2020.

*7. FDA, Guidance for Industry and Review Staff, "Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities--Questions and Answers," June 2018 (available at https://www.fda.gov/media/102683/download), accessed February 5, 2020.

*8. FDA, Guidance for Industry, "Industry-Supported Scientific and Educational Activities," December 1997 (available at https://www.fda.gov/media/70844/download), accessed February 5, 2020.

*9. FDA, Draft Guidance for Industry, "Distributing Scientific and Medical Publications on Unapproved New Uses--Recommended Practices," February 2014 (available at https://www.fda.gov/media/88031/download), accessed February 5, 2020.

*10. FDA, Draft Guidance for Industry, "Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices," December 2011 (available at https://www.fda.gov/media/82660/download), accessed February 5, 2020.

11. Eguale, T., D.L. Buckeridge, A. Verma, et al., "Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population," Journal of American Medical Association Internal Medicine, 176(1):55–63, 2016.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 801

Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR parts 201 and 801 be amended as follows:

PART 201--LABELING

1. The authority citation for part 201 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 343, 351, 352, 353, 355, 358, 360, 360b, 360ccc, 360ccc-1, 360ee, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

2. Revise § 201.128 to read as follows:

§ 201.128 Meaning of *intended uses*.

The words *intended uses* or words of similar import in §§ 201.5, 201.115, 201.117, 201.119, 201.120, 201.122, and 1100.5 of this chapter refer to the objective intent of the persons legally responsible for the labeling of an article (or their representatives). The intent may be shown by such persons' expressions, the design or composition of the article, or by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. Objective intent may be shown, for example, by circumstances in which the article is, with the knowledge of such persons or their representatives, offered or used for a purpose for which it is neither labeled nor advertised; provided, however, that a firm

would not be regarded as intending an unapproved new use for an approved drug based solely on that firm's knowledge that such drug was being prescribed or used by health care providers for such use. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he or she received the article, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses.

PART 801--LABELING

3. The authority citation for part 801 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 360d, 360i, 360j, 371, 374.

4. Revise § 801.4 to read as follows:

§ 801.4 Meaning of *intended uses*.

The words *intended uses* or words of similar import in §§ 801.5, 801.119, 801.122, and 1100.5 of this chapter refer to the objective intent of the persons legally responsible for the labeling of an article (or their representatives). The intent may be shown by such persons' expressions, the design or composition of the article, or by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. Objective intent may be shown, for example, by circumstances in which the article is, with the knowledge of such persons or their representatives, offered or used for a purpose for which it is neither labeled nor advertised; provided, however, that a firm would not be regarded as intending an unapproved new use for an approved or cleared device based solely on that firm's knowledge that such device was being prescribed or used by health care providers for such use.

The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he or she received the article, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses.

Dated: _____.

_____