



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 801, and 1100

[Docket No. FDA-2015-N-2002]

RIN 0910-AH19

Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding “Intended Uses”

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing this final rule to describe the circumstances in which a product made or derived from tobacco that is intended for human consumption will be subject to regulation as a drug, device, or a combination product under the Federal Food, Drug, and Cosmetic Act (the FD&C Act). This action is intended to provide direction to regulated industry and to help avoid consumer confusion.

DATES: This rule is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: For access to the docket to read background documents or comments received, go to <https://www.regulations.gov> and insert the docket number found in brackets in the heading of this final rule into the “Search” box and follow the prompts, and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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Executive Summary

Purpose of the Rule

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) amends the FD&C Act and provides FDA with the authority to regulate tobacco products. Section 201(rr) of the FD&C Act (21 U.S.C. 321(rr)), as amended by the Tobacco Control Act, defines the term “tobacco product” as any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product). Excluded from the definition of a tobacco product is any article that is a drug, device, or combination product. Any article that is a drug, device, or combination product will be regulated as such rather than as a tobacco product.

Because some ambiguity surrounds the circumstances under which a product that is made or derived from tobacco would be regulated as a drug, device, or combination product, and the circumstances under which it would be regulated as a tobacco product, FDA is taking this action to provide clarity regarding our interpretation of the drug and device definitions in the FD&C Act with respect to products made or derived from tobacco. This final rule will provide assistance for entities intending to market products made or derived from tobacco. FDA expects the rule will also assist investigators planning to use products made or derived from tobacco for an investigational use in determining the investigational use requirements that apply to their proposed studies. The final rule is also intended to increase clarity regarding the intended uses and supporting evidence that make a product made or derived from tobacco subject to regulation as a drug, device, or combination product, helping consumers distinguish products made or derived from tobacco that are intended for medical use from products marketed for other uses.

In addition, FDA is taking the opportunity to make changes to existing regulations at §§ 201.128 and 801.4 (21 CFR 201.128 and 801.4), and to conform them to how the Agency currently applies these regulations to drugs and devices generally.

#### Summary of the Major Provisions of the Regulatory Action

Conceptually, the final rule follows the disease prong and the structure/function prong (with certain specified limitations) of the statutory definitions of “drug” and “device” (section 201(g) and (h) of the FD&C Act). Under the final rule, a product made or derived from tobacco and intended for human consumption is regulated as a drug, device, or combination product in two circumstances: (1) If the product is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease; or (2) if the product is intended to affect the structure or any function of the body in any way that is different from

effects related to nicotine that were commonly and legally claimed in the marketing of cigarettes and smokeless tobacco products prior to March 21, 2000. The final rule also clarifies remaining circumstances where a product is subject to regulation as a tobacco product.

In addition, FDA is amending its existing intended use regulations for drugs and devices by inserting in §§ 201.128 and 801.4 a reference to the final rule to clarify the interplay between these regulations and this final rule. FDA has made further changes to conform §§ 201.128 and 801.4 to reflect how the Agency currently applies them to drugs and devices.

#### Costs and Benefits

The final rule clarifies the regulatory status of products made or derived from tobacco and our interpretation and application of the existing intended use regulations. This will reduce the ambiguity and may create some efficiency gains associated with submitting an application for approval or marketing authorization of a new tobacco-derived product, or with initiating research for a new tobacco-derived product. In addition, we assume that the regulation will clarify for consumers when products made or derived from tobacco are intended for medical uses rather than for other uses.

We assume that all tobacco-derived product manufacturers would incur one-time costs to learn the rule. There may also be a one-time cost incurred by a small number of manufacturers of tobacco products to review and revise product communications such as labeling and associated promotional materials. The following table reports these one-time costs.

Table 1.--One-Time Costs

	Low	Mid-Point	High
Learning costs	\$117,412	\$146,779	\$176,147
Review communications, such as labeling and promotional materials	\$486,024	\$486,024	\$486,024
Revisions to communications, such as labeling and promotional materials	\$283,003	\$1,092,422	\$1,901,841
Total	\$886,439	\$1,725,225	\$2,564,012

## I. Background

In the Federal Register of September 25, 2015 (80 FR 57756), FDA issued a proposed rule entitled “Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding ‘Intended Uses.’” We received over 1,900 comments on the proposed rule. Two comments requested that the comment period be extended due to the complexity of the legal issues involved. One of these comments related to the original 60-day comment period. In the Federal Register of November 30, 2015 (80 FR 74737), FDA reopened the comment period for an additional 30 days. The second comment appears to relate to the additional 30-day comment period announced in 80 FR 74737. With respect to the comment requesting an extension beyond the additional 30-day comment period, FDA believes this comment to be misplaced as it generally references “nine questions” that are related to a different rulemaking--the proposed version of the deeming rule.<sup>1</sup>

### A. Definition of “Tobacco Product”

The Tobacco Control Act was enacted on June 22, 2009 (Pub. L. 111-31), amending the FD&C Act and providing FDA with the authority to regulate tobacco products. Section 101(a) of the Tobacco Control Act amends section 201 of the FD&C Act by adding paragraph (rr), which defines the term “tobacco product.” In general, a “tobacco product” is defined as any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product). Section 201(rr)(2) of the FD&C Act excludes from the definition of a tobacco product any article that is defined as

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<sup>1</sup> "Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products; Proposed Rule" (79 FR 23142, April 25, 2014).

a drug under section 201(g)(1), a device under section 201(h), or a combination product described in section 503(g) of the FD&C Act (21 U.S.C 353(g)). Section 201(rr)(3) of the FD&C Act explains that any article that is a drug, device, or combination product shall be subject to chapter V of the FD&C Act (the authorities for drugs and devices) rather than chapter IX (the authorities for tobacco products).<sup>2</sup>

## B. Drug/Device/Combination Product Definitions

### 1. Medical Product Definitions

As noted in section I.A, the definition of “tobacco product” excludes anything that is a “drug,” “device,” or “combination product” under the FD&C Act. The FD&C Act defines “drug” (in relevant part) as an article intended either: (1) For use in the diagnosis, cure, mitigation, treatment, or prevention of disease (referred to as the “disease prong” of the definition) or (2) to affect the structure or any function of the body (the “structure/function prong”) (section 201(g)(1) of the FD&C Act). The FD&C Act defines a “device” (in relevant part) as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, intended either: (1) For use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease or (2) to affect the structure or any function of the body, and which does not achieve its primary intended purposes through chemical action within or on the body of man and which is not dependent on being metabolized for the achievement of its primary intended purposes (section 201(h) of the FD&C Act).<sup>3</sup> Combination products are products that constitute a combination of a drug, device, or biological product (section 503(g) of the FD&C Act). Under

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<sup>2</sup> Section 201(rr)(4) of the FD&C Act prohibits a tobacco product from being marketed in combination with any other article or product regulated under the FD&C Act. This rulemaking did not address section 201(rr)(4).

<sup>3</sup> In this final rule, the cited language may be referred to as the “drug/device definitions.”

the FD&C Act, the Secretary's determination of the primary mode of action of a combination product determines which Center at FDA will have primary jurisdiction over the product (section 503(g) of the FD&C Act).

FDA had previously interpreted the exclusion in the tobacco product definition to mean that if a product made or derived from tobacco is determined to have a drug or device "intended use," it will be regulated as a medical product, not as a tobacco product. As discussed in greater detail in this document, this interpretation was qualified in Sottera, Inc. v. Food & Drug Administration, 627 F.3d 891 (D.C. Cir. 2010), in which the D.C. Circuit applied the holding of Food & Drug Administration v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 156 (2000), to all tobacco products. Thus, the determination of whether a product is a medical product or a tobacco product is based on the FD&C Act and associated regulations and also takes into account relevant legal precedent (further described in section I.D).

## 2. How Intended Use Is Determined

In determining a product's intended use, the Agency may look to "any...relevant source," including but not limited to the product's labeling, promotional claims, and advertising (see, e.g., Action on Smoking and Health v. Harris, 655 F.2d 236, 239 (D.C. Cir. 1980); United States v. Storage Spaces Designated Nos. "8" and "49," 777 F.2d 1363, 1366 (9th Cir. 1985), Hanson v. United States, 417 F. Supp. 30, 35 (D. Minn.), aff'd, 540 F.2d 947 (8th Cir. 1976)).



For example, FDA may take into account any claim or statement made by or on behalf of a manufacturer that explicitly or implicitly promotes a product for a particular use (see, e.g., § 201.128 (drugs), § 801.4 (devices)).<sup>4</sup>

To establish a product's intended use, FDA is not bound by the manufacturer or distributor's subjective claims of intent, but rather can consider objective evidence, which may include a variety of direct and circumstantial evidence. Thus, FDA may also take into account any circumstances surrounding the distribution of the product or the context in which it is sold (see *id.*; see also United States v. Travia, 180 F.Supp.2d 115, 119 (D.D.C. 2001)). In the context of medical products, generally, circumstantial evidence often ensures that FDA is able to pursue firms that attempt to evade FDA medical product regulation by avoiding making express claims about their products. As FDA has previously stated, however, the Agency would not, absent extraordinary circumstances, regard a firm as intending an unapproved new use for an approved drug, or a device that has been approved, cleared, granted marketing authorization, or is exempt from premarket notification requirements (for ease of reference, such a device is referred to as "an approved or cleared device" (or similar terms) throughout this preamble) based solely on the firm's knowledge that such product was being prescribed or used by doctors for such use (Ref. 1).

Thus, when a product made or derived from tobacco is marketed or distributed for an intended use that falls within the drug/device definitions, it is regulated as a medical product, subject to the limitations discussed further in this document. Courts have recognized that products made or derived from tobacco marketed with "disease" claims and certain

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<sup>4</sup> Under FDA regulations, the term "intended use" relates to the objective intent of the medical product manufacturer, packer, distributor, or seller, including both corporate entities and natural individuals (hereinafter "manufacturers" or "firms").

“structure/function” claims are drugs (see United States v. 46 Cartons...Containing Fairfax Cigarettes, 113 F.Supp. 336, 337, 338 (D. N.J. 1953) (cigarettes marketed for the prevention of respiratory diseases); United States v. 354 Bulk Cartons...Trim Reducing-Aid Cigarettes, 178 F.Supp. 847, 851 (D. N.J. 1959) (cigarettes marketed for weight reduction)).

### C. Comments and Responses Regarding Definitions

Comments were received from tobacco product manufacturers, retailers, academia, medical professionals, advocacy groups, and consumers. To make it easier to identify comments and our responses, the word “Comment,” in parentheses, will appear before each comment, and the word “Response,” in parentheses, will appear before each response. We have numbered the comments to make it easier to distinguish between comments; the numbers are for organizational purposes only and do not reflect the order in which we received the comments or any value associated with them. We have combined similar comments under one numbered comment. In addition to the comments specific to this rulemaking that we address in the following paragraphs, we received many general comments expressing support or opposition to the rule. These comments express broad policy views and do not address specific points related to this rulemaking. Therefore, these general comments do not require a response. Other comments outside the scope of this rulemaking also have not been addressed here. Summaries of the remaining comments, as well as FDA’s responses, are included in this document.

(Comment 1) At least one comment stated that FDA is not permitted to regulate the nicotine in cigarettes as a drug and should not be permitted to regulate electronic nicotine delivery systems (ENDS) as medical products.

(Response) FDA disagrees. Section 201(g) of the FD&C Act defines “drug” as articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or

other animals, and articles (other than food) intended to affect the structure or any function of the body of man or other animals. Section 201(h) of the FD&C Act defines “device” (in relevant part) as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory,” that is intended “for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or . . . to affect the structure or any function of the body,” and which does not achieve its primary intended purposes through chemical action within or on the body of man and which is not dependent on being metabolized for the achievement of its primary intended purposes. As explained in this final rule, FDA has the authority to regulate a product made or derived from tobacco, including cigarettes and ENDS, as a medical product if it is distributed or marketed for an intended use that falls within the drug/device definitions, unless the product is intended to affect the structure or any function of the body in any way related to the effects of nicotine that were commonly and legally claimed in the marketing of cigarettes and smokeless tobacco products prior to March 21, 2000.

(Comment 2) Several comments stated that there is no need to clarify the medical product and tobacco product definitions that govern FDA regulation of these products. One of those comments also went on to state that there is a clear difference between drug product claims and “consumer-oriented marketing statements” about smoking cessation.

(Response) FDA disagrees that there is no need for additional clarity in this area. The Agency frequently receives inquiries regarding jurisdictional distinctions for products made or derived from tobacco, and given the broad range of intended uses for products made or derived from tobacco and the increasing variety of such products on the market, FDA believes that the potential for consumer confusion is increasing. This is especially true when tobacco-derived

products that may otherwise appear to be products intended for recreational use make claims related to quitting smoking and treatment of nicotine addiction.

FDA considers claims about smoking cessation to be more than simply “consumer-oriented marketing statements.” As noted in the preamble to the proposed rule, claims related to smoking cessation have long been recognized as evidence of intended use, conferring drug or device jurisdiction, and smoking cessation claims also have long been associated with the intended uses of curing or treating nicotine addiction and its symptoms. For example, smoking cessation claims have appeared on the approved labeling for nicotine replacement therapies since the mid-1990s. FDA believes it is important to clarify and reiterate that smoking cessation claims on any product can render that product subject to FDA’s medical products authorities.

(Comment 3) Comments had differing opinions on whether ENDS meet the definition of “tobacco product” as defined in the FD&C Act. Several comments stated that ENDS fall under the definition of “tobacco product” as defined in the FD&C Act if they contain nicotine derived from tobacco and are not intended to be drugs or devices. However, other comments stated that ENDS, including vaping hardware, do not fall within the definition of “tobacco product.”

(Response) FDA agrees that ENDS meet the definition of “tobacco product” if they are not drugs, devices, or combination products. The term “tobacco product” is defined in section 201(rr) of the FD&C Act (21 U.S.C. 321(rr)) to mean any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product), and excluding drugs, devices, and combination products as defined under the FD&C Act. Unless they are marketed for an intended use that falls within the drug/device definitions, ENDS products meet the definition of tobacco

product. Additionally, as discussed elsewhere in the preamble, if ENDS products are intended to affect the structure or function of the body in any way related to the effects of nicotine that were commonly and legally claimed in the marketing of cigarettes and smokeless tobacco products prior to March 21, 2000, they will be regulated as tobacco products. (See section II.C.)

FDA disagrees with comments stating that vaping hardware does not fall within the definition of “tobacco product.” As the Agency explained in the final deeming regulation<sup>5</sup>, the definition of tobacco product includes components and parts. Also included in the final deeming regulation is a non-exhaustive list of examples of components and parts used with ENDS products. Examples of components and parts used with ENDS products includes, but are not limited to: E-liquids; atomizers; batteries (with or without variable voltage); cartomizers (atomizer plus replaceable fluid-filled cartridge); digital display/lights to adjust settings; clearomisers, tank systems, flavors, vials that contain e-liquids, and programmable software. Thus, vaping hardware meets the definition of tobacco product.

#### D. History of 1996 Rulemaking and Relevant Litigation

Although the courts have recognized that tobacco-derived products can be regulated as medical products under the FD&C Act in certain circumstances, courts have also held that there are limitations on how the drug and device definitions can be applied to products made or derived from tobacco. This section provides a summary of FDA regulatory action and related litigation relevant to those limitations.

In 1996, FDA issued a regulation restricting the sale and distribution of cigarettes and smokeless tobacco to children and adolescents (the 1996 rule) (61 FR 44396, August 28, 1996).

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<sup>5</sup> “Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products; Final Rule” (81 FR 28973, May 10, 2016).

This rule included FDA's determination that it had jurisdiction over cigarettes and smokeless tobacco under the FD&C Act. The basis for this determination was that cigarettes and smokeless tobacco were intended to affect the structure or function of the body, within the FD&C Act definitions of the terms "drug" and "device," because nicotine has significant pharmacological effects. In addition, FDA found that cigarettes and smokeless tobacco were combination products consisting of the drug nicotine and device components intended to deliver nicotine to the body. In the 1996 rule, FDA concluded that cigarettes and smokeless tobacco should be regulated under the device authorities of the FD&C Act. The 1996 rule was challenged in court by a group of tobacco manufacturers, retailers, and advertisers on the grounds that FDA lacked jurisdiction to regulate tobacco products "as customarily marketed;" that the regulations exceeded FDA's authority to regulate devices; and that the advertising restrictions violated the First Amendment.

The Supreme Court struck down the 1996 rule in Food & Drug Administration v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 156 (2000), holding that FDA lacked jurisdiction over tobacco products "as customarily marketed." The Court found that Congress intended to exclude tobacco products from FDA's jurisdiction. In Brown & Williamson, the Court determined that tobacco products could not be made safe and effective for their intended uses, and therefore, if FDA had authority over them, FDA would have to remove them from the market, but that Congress had foreclosed such action (529 U.S. at 135-139). The Court also observed that Congress, in enacting statutes to regulate the labeling and advertising of conventional tobacco products, such as cigarettes and smokeless tobacco, had "effectively ratified FDA's long-held position" that the Agency lacked jurisdiction to regulate tobacco products "absent claims of therapeutic benefit by the manufacturer" (529 U.S. at 144).

In 2008 and early 2009, FDA detained multiple shipments of electronic cigarettes from overseas manufacturers and denied them entry into the United States on the ground that electronic cigarettes were unapproved drug-device combination products under the FD&C Act. In April 2009, two of the importers who were affected by this action sought a preliminary injunction to enjoin FDA from regulating electronic cigarettes as drug-device combination products and from denying entry of those products into the United States.<sup>6</sup> Between the filing of the lawsuit and a decision on the motion for a preliminary injunction, Congress passed the Tobacco Control Act and the President signed it into law. The District Court subsequently granted a preliminary injunction, relying on Brown & Williamson and the recently enacted Tobacco Control Act (Smoking Everywhere, Inc. v. FDA, 680 F. Supp. 2d 62 (D.D.C. 2010)). FDA appealed the decision and the United States Court of Appeals for the District of Columbia Circuit (D.C. Circuit) affirmed in Sottera, Inc. v. Food & Drug Administration, 627 F.3d 891 (D.C. Cir. 2010).<sup>7</sup> The D.C. Circuit determined that the decision in Brown & Williamson was not limited to tobacco products that were the subject of the specific federal legislation discussed in that case. The D.C. Circuit found that under the Tobacco Control Act, all products made or derived from tobacco and intended for human consumption that are “marketed for therapeutic purposes” are subject to FDA’s drug and/or device provisions, whereas “customarily marketed tobacco products” are subject to regulation as “tobacco products” (Sottera, 627 F.3d at 898-899; see also Brown & Williamson, 529 U.S. at 144-156).

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<sup>6</sup> The original district court case was filed by Smoking Everywhere, Inc., and the case was joined by Sottera, Inc., which does business as NJOY.

<sup>7</sup> On January 24, 2011, the D.C. Circuit denied the government’s petitions for rehearing and rehearing en banc (by the full court). See Sottera v. Food & Drug Administration, No. 10-5032 (D.C. Cir. Jan. 24 2011) (per curiam).

The Court in Brown & Williamson frequently referred to “tobacco products as customarily marketed,” but never defined that phrase. The Court contrasted that phrase with “claims of therapeutic benefit” (see, e.g., 529 U.S. at 127, 158), which it also did not define, although it did indicate that tobacco products’ purported “therapeutic benefits” included all four of the structure/function intended uses on which FDA had based its 1996 rulemaking: Satisfying addiction, stimulation, sedation, and weight control (529 U.S. at 141). Neither of these terms is used in the FD&C Act. In Sottera, the D.C. Circuit relied on Brown & Williamson and repeated these phrases in describing contrasting types of products. The court in Sottera specifically equated “therapeutic uses” with the disease prong of the drug/device definitions in the FD&C Act and said that customarily marketed tobacco products were sold without therapeutic claims (627 F.3d at 894) and should be regulated as tobacco products under the FD&C Act, as amended by the Tobacco Control Act. As noted, the Brown & Williamson decision indicated that the four intended structure/function effects FDA had identified (satisfying addiction, stimulation, sedation, and weight control) were purported tobacco product “therapeutic benefits” (Brown & Williamson, 529 U.S. at 141). But neither the Brown & Williamson nor the Sottera court defined what might constitute claims of therapeutic benefit, nor did they explain the relationship between “tobacco products as customarily marketed” and the structure/function prong of the drug/device definitions of the FD&C Act. In addition, no court has addressed whether certain structure/function claims for products made or derived from tobacco that generally were not made for “tobacco products as customarily marketed” should be treated as drug or device claims.<sup>8</sup>

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<sup>8</sup> In Sottera, there are a few instances where the court’s opinion could be read to suggest that all products made or



## II. Purpose of Regulatory Action

Because some ambiguity surrounds the circumstances under which a product that is made or derived from tobacco would be regulated as a drug, device, or combination product, and the circumstances under which it would be regulated as a tobacco product, we are issuing this final rule to provide clarity regarding our interpretation of the drug/device definitions in the FD&C Act with respect to products made or derived from tobacco. We believe that this final regulation will provide assistance for entities intending to market products made or derived from tobacco and for entities that plan to study these products. For example, the rule is expected to help sponsors determine which FDA Center should be consulted as they develop their products and make appropriate premarket submissions to bring new products to market. FDA expects the rule will also assist investigators planning to use products made or derived from tobacco for an investigational use in determining the investigational use requirements that apply to their proposed studies. In addition, we believe it is important to avoid consumer confusion about which products are intended for medical uses versus recreational or other uses. The rule is expected to increase clarity regarding the types of intended uses and supporting evidence that make a product made or derived from tobacco subject to regulation as a drug or device, which we expect will help consumers distinguish products made or derived from tobacco that are intended for medical use from products marketed for other uses. Finally, the rule is intended to provide clarity for drug and device manufacturers generally regarding FDA's interpretation and application of its existing intended use regulations.

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derived from tobacco “marketed without claims of therapeutic effect” are, ipso facto, tobacco products “as customarily marketed” (627 F.3d at 895; see also *id.* at 898-899). However, because the issue of drug/device jurisdiction over structure/function intended uses that are not related to the commonly understood effects of nicotine was not before the court, this reading--even if it were correct--would be dicta.

In both the Brown & Williamson and Sottera decisions, the courts set forth (but did not define) two poles--“tobacco products as customarily marketed” and “claims of therapeutic benefit”--and found that the “customarily marketed” pole was not within FDA’s drug/device jurisdiction, but that the “claims of therapeutic benefit” pole was within FDA’s drug/device jurisdiction. As noted in section I.D, the terminology used by the courts in establishing these two poles is not the terminology used by the FD&C Act in defining drugs and devices. Instead, the FD&C Act’s drug and device definitions reference, in relevant part, diagnosis, cure, mitigation, treatment, or prevention of disease (disease prong) and effects on the structure or any function of the body (structure/function prong). In addition, while certain products and claims may fall clearly at one pole or the other, a spectrum of products and claims may fall somewhere between the two poles. In the sections that follow, we describe our interpretation of the jurisdictional lines established by the FD&C Act’s drug, device, and tobacco product definitions as informed by the decisions in Brown & Williamson and Sottera.

A. Intended Uses For Products Made or Derived From Tobacco That Bring Products Within the Disease Prong

1. Intended Uses That Bring Products Within the Disease Prong

As discussed in section I.B, articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease are drugs, devices, or combination products under the FD&C Act. Products made or derived from tobacco have historically been regulated as medical products when they are marketed for intended uses that fall within the disease prong. For example, FDA has approved a number of drug products made or derived from tobacco as nicotine replacement therapies with indications to reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking. Accordingly, FDA has long considered

claims related to smoking cessation in the context of curing or treating nicotine addiction and its symptoms to bring products within FDA's "disease prong" jurisdiction.

FDA has also taken enforcement action against products made or derived from tobacco that were marketed with claims of therapeutic benefit but that did not have approved new drug applications (NDAs). For example, FDA seized cigarettes on the grounds that they were misbranded drugs when the manufacturer represented that the cigarettes were effective in preventing respiratory diseases, common cold, influenza, pneumonia, and various other ailments (United States v. 46 Cartons...Containing Fairfax Cigarettes, 113 F.Supp. 336, 337, 338 (D. N.J. 1953)); see also United States v. 354 Bulk Cartons Trim Reducing-Aid Cigarettes, 178 F. Supp. 847 (D. N.J. 1959) (similar, where manufacturer made weight-reduction claims for its cigarettes).

The "claims of therapeutic benefit" language used by the Brown & Williamson and Sottera courts has a logical relationship to the disease prong of the drug/device definition, in that "therapeutic" can be defined as "relating to the treatment of disease or disorders by remedial agents or methods" or to "providing or assisting in a cure."<sup>9</sup> With this rule, FDA is clarifying the categories of claims relevant to products made or derived from tobacco that FDA considers to be evidence of intended use that brings products within the disease prong in light of the Sottera and Brown & Williamson decisions. As discussed previously, claims related to smoking cessation have long been recognized as evidence of intended use conferring drug or device jurisdiction. Smoking cessation claims have also long been associated with intended uses of curing or treating nicotine addiction and its symptoms. For example, the approved labeling for nicotine

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<sup>9</sup> See, e.g., Merriam-Webster Online Dictionary, available at <http://www.merriam-webster.com/dictionary/therapeutic>.

replacement therapies includes the following statements: “Purpose: Stop smoking aid; Use: reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking.”<sup>10</sup>

Against this backdrop, smoking cessation claims on any product generally create a strong suggestion of intended therapeutic benefit to the user that generally will be difficult to overcome absent clear context indicating that the product is not intended for use to cure or treat nicotine addiction or its symptoms, or for another therapeutic purpose.

Given the availability of FDA-approved drugs for smoking cessation, FDA believes that consumers are particularly susceptible to confusion where products made or derived from tobacco that otherwise appear to be products intended for recreational use make claims related to quitting smoking. Therefore, FDA considers claims related to smoking cessation to require careful scrutiny. Where products making claims related to quitting smoking also attempt to disclaim that use in some way, FDA intends to view such disclaimers skeptically because of the likelihood of consumer confusion. In most cases, as discussed in more detail in response to Comment 13, FDA does not believe that disclaimers will sufficiently mitigate consumer confusion due to the product’s claimed therapeutic benefit.

FDA will treat several other categories of claims for products made or derived from tobacco as evidence of intended use that brings the products within the disease prong of the drug/device definition. These categories of claims are discussed further in section IV, Description of the Final Rule). We note that sections 911(c) and 918 of the FD&C Act (21 U.S.C. 387k(c) and 387r), as amended by the Tobacco Control Act, contemplate that products

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<sup>10</sup> See, e.g., approved labeling for Nicoderm CQ, Nicorette, Habitrol.

intended for the treatment of tobacco dependence and for relapse prevention, among other things, may be subject to FDA's drug/device jurisdiction.

## 2. Distinction Between Modified Risk Claims and Claims That Are Evidence of Disease-Prong Intended Uses

With this final rule, FDA is also clarifying the relationship between FDA's regulation of a certain category of tobacco products--modified risk tobacco products (MRTPs)--and FDA's regulation of medical products that are intended to mitigate disease. MRTPs are tobacco products that are sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products (section 911(b)(1) of the FD&C Act). Tobacco products that are sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products means a tobacco product:

(1) That represents in its label, labeling, or advertising, either implicitly or explicitly, that:

- The tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;
- the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or
- the tobacco product or its smoke does not contain or is free of a substance;

(2) That uses the descriptors "light," "mild," "low," or similar descriptors in its label, labeling, or advertising; or

(3) For which the tobacco product manufacturer has taken any action directed to consumers through the media or otherwise, other than by means of the tobacco product's label, labeling, or advertising, after June 22, 2009, respecting the product that would be reasonably

expected to result in consumers believing that the tobacco product or its smoke may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products, or presents a reduced exposure to, or does not contain or is free of, a substance or substances.

See section 911(b)(2) of the FD&C Act.<sup>11</sup>

Because MRTPs have the potential to be marketed as less harmful than other tobacco products, including as presenting a lower risk of tobacco-related disease than another tobacco product, FDA recognizes that there might be questions about how these products relate to FDA's medical product jurisdiction over products made or derived from tobacco that are intended for use in disease mitigation and prevention. MRTPs may have the ultimate effect of lowering disease risk for users who would otherwise use another, more harmful tobacco product. However, an important distinction between MRTPs and medical products is that, while medical products approved/cleared for disease mitigation or prevention act affirmatively to combat a disease or health condition, MRTPs present relatively less risk of disease (e.g., by presenting reduced exposure to harmful constituents relative to another tobacco product), but do not affirmatively act to mitigate, prevent, or otherwise treat disease. In addition, while medical products approved for disease mitigation are determined to be both safe and effective for their approved use, MRTPs are reviewed based, in part, on a "benefit the health of the population as a whole" standard, and like other tobacco products, still expose users to inherent (if reduced) harms.

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<sup>11</sup> No smokeless tobacco product shall be considered to be sold or distributed for use to reduce harm or the risk of tobacco-related disease solely because its label, labeling, or advertising uses the following phrases: "smokeless tobacco," "smokeless tobacco product," "not consumed by smoking," "does not produce smoke," "smokefree," "smoke-free," "without smoke," "no smoke," or "not smoke" (section 911(b)(2)(C) of the FD&C Act).

For purposes of illustration, claims of modified risk might include claims like “contains less nicotine than [tobacco product X]”, “using [MRTP] reduces your risk of lung cancer compared to using [tobacco product X]”, and “lower level of nitrosamines than other smokeless tobacco products.” In contrast, a claim that a product “inhibits the progression of disease in adult patients with chronic obstructive pulmonary disease” is evidence of intended uses that would bring the product within drug/device jurisdiction.

#### B. Comments and Responses Regarding Modified Risk Tobacco Products

(Comment 4) At least one comment remarked that research studies and public opinion may come to reflect that a tobacco product appears to have properties similar to those of a medical drug or MRTP. The comment asserted that acceptance of these properties by the scientific and medical community or by the public should not subject the product to regulation as a medical product or MRTP in the absence of any specific claims by the manufacturer.

(Response) As explained in this final rule, with certain exceptions, products made or derived from tobacco are subject to regulation as medical products if they are distributed for an intended use that falls within the FD&C Act’s drug/device definitions, and the Agency may look to any relevant source to determine intended use. To the extent this comment suggests that manufacturer claims are always necessary to establish a medical product’s intended use, FDA disagrees. As discussed at various points in this final rule (for example, in response to Comment 18), FDA is not bound by the manufacturer or distributor’s subjective claims of intent, but rather can consider objective evidence, which may include a variety of direct and circumstantial evidence. Nevertheless, FDA agrees with the comment that neither the opinions of the scientific and medical communities nor public opinion considered alone should dictate when a product made or derived from tobacco is regulated as a medical product or MRTP. In general, FDA

would not regard a manufacturer as intending a medical use for a product made or derived from tobacco based solely on study findings or widespread belief that the product appears to have properties similar to those of a medical product. Similarly, FDA would not regard a manufacturer of a product made or derived from tobacco as selling or distributing a product for use to reduce harm or the risk of tobacco-related disease based solely on study findings or widespread belief that the product appears to have properties similar to those of an MRTP.

C. Intended Uses For Products Made or Derived From Tobacco That Bring Products Within the Structure/Function Prong

As discussed in section I.B, the drug/device definitions in the FD&C Act include articles “intended to affect the structure or any function of the body,” and FDA’s assertion of jurisdiction over cigarettes and smokeless tobacco in 1996 was predicated on the pharmacological effects of nicotine on the structure or function of the body. In addition, as explained previously, the Court in Brown & Williamson rejected that assertion of jurisdiction, finding that Congress did not intend for FDA to have jurisdiction over cigarettes “as customarily marketed.”

Based on the Brown & Williamson holding and the Sottera court’s application of that holding to all tobacco products, it is necessary to determine whether the intended use of a product made or derived from tobacco was the subject of claimed structure or function effects for tobacco products “as customarily marketed”--and therefore outside of FDA’s drug/device jurisdiction. FDA believes the appropriate inquiry is whether the intended structure/function effects relate to effects of nicotine that were commonly and legally claimed in the marketing of cigarettes and smokeless tobacco products prior to the date of the Supreme Court’s decision in Brown & Williamson (March 21, 2000).



For example, as discussed in the 1996 rulemaking, claims related to satisfaction, pleasure, enjoyment, and refreshment are euphemisms for the delivery of a pharmacologically active dose of nicotine and thus relate to effects on the structure or function of the body (61 FR 44396 at 45101 and 45175-45178). Nonetheless, FDA does not consider these tobacco satisfaction and enjoyment claims to bring products within its drug and device regulatory authority because these are structure/function claims related to the effects of nicotine and were commonly and legally made before March 21, 2000. Similarly, FDA does not consider claims suggesting that a tobacco product provides an alternative way of obtaining the effects of nicotine, or that a tobacco product will provide the same effects as another tobacco product--such as “satisfying smoking alternative,” “provides all the pleasure of smoking,” “get your nicotine fix,” or “provides smokers the same delight, physical and emotional feelings”--to bring a tobacco product within its drug and device authority.

The Brown & Williamson and Sottera decisions do not reach the issue of intended uses that fall outside the disease prong of the drug/device definition and that are outside the area of “customarily marketed” tobacco product claims. FDA believes certain structure/function intended uses for products made or derived from tobacco continue to fall within our drug/device regulatory authority. FDA believes these structure/function intended uses fall into two main categories: (1) Intended uses that are unrelated to the pharmacological effects of nicotine and (2) intended uses that were not the subject of claims that were commonly and legally made for cigarettes and smokeless tobacco products (i.e., the products addressed in the 1996 rule) prior to the Supreme Court’s decision in Brown & Williamson. Thus, to the extent manufacturers intend products made or derived from tobacco to be used to affect the structure or function of the body in any way that is not related to the effects of nicotine that were commonly and legally claimed

in the marketing of cigarettes and smokeless tobacco products prior to March 21, 2000, FDA would consider these intended uses to remain within its drug/device jurisdiction under the final rule. For example, FDA's 1996 rulemaking identified "sedation," "stimulation," and "weight loss" as intended structure/function effects related to nicotine in cigarettes and smokeless tobacco products (61 FR 44396 at 44667; see also Brown & Williamson, 529 U.S. at 127). These structure/function effects are similar to "relieve tension," "restore mental alertness," and "promote weight loss," which the proposed rule gave as examples of potential intended structure/function effects (80 FR 57756 at 57760; see also Comment 7 in this document). But absent evidence that "sedation," "stimulation," or "weight loss" is both a structure/function effect related to nicotine and was commonly and legally claimed in marketing cigarettes or smokeless tobacco products prior to March 21, 2000, FDA will consider products made or derived from tobacco, whose intended use includes such structure/function effects, to be medical products.

Similarly, "maintain memory"--another example of a potential intended structure/function effect mentioned in the proposed rule (80 FR 57756 at 57760)--was (as FDA's 1996 rulemaking observed) a pharmacological effect that Philip Morris researchers attributed to nicotine and that R.J. Reynolds Tobacco asserted as a "benefit" in court filings (61 FR 44396 at 44857-44858 and 45029). But once again, absent evidence that "maintaining memory" is both a structure/function effect related to nicotine, and was commonly and legally claimed in marketing cigarettes or smokeless tobacco products prior to March 21, 2000, FDA will consider products made or derived from tobacco, intended for use to "maintain memory," to be medical products.

Different facts but a similar analysis apply to the proposed rule's other examples of potential intended structure/function effects, "maintain healthy lung function" and "support the immune system." (80 FR 57760). In contrast to its findings for "stimulation," "sedation," and

“weight loss,” (61 FR 44396 at 44667), FDA’s 1996 rulemaking did not identify “maintain healthy lung function” or “support the immune system” as intended structure/function effects of cigarettes or smokeless tobacco products. But as with those other potential intended uses, absent evidence that “maintaining healthy lung function” or “supporting the immune system” are both structure/function effects related to nicotine, and were commonly claimed in marketing cigarettes or smokeless tobacco products prior to March 21, 2000, FDA will consider products made or derived from tobacco, intended for use to achieve such structure/function effects, to be medical products.

FDA believes that it is important to recognize structure/function intended uses that were not commonly and legally claimed in the marketing of cigarettes and smokeless tobacco products prior to the decision in Brown & Williamson. Structure/function intended uses are a longstanding and important aspect of FDA’s medical product jurisdiction, grounded in the statutory definitions of “drug” and “device” in the FD&C Act. We recognize that products made or derived from tobacco are unique because of the regulatory regime for tobacco products under the FD&C Act, and that some products made or derived from tobacco making certain structure/function claims are now outside our drug/device jurisdiction. However, we believe it is consistent with the FD&C Act, case law, and our public health mission to determine that medical products include products made or derived from tobacco whose intended use includes effects on the structure or function of the body that are distinct from the pharmacological effects related to nicotine that were commonly and legally claimed before March 21, 2000.

FDA believes this final rule will provide clarity to manufacturers about how products made or derived from tobacco will be regulated if they are marketed or distributed for certain intended uses. This clarification will allow regulated industry to plan accordingly during the

product development and postmarketing phases and will help researchers understand the applicable regulatory requirements associated with the investigational use of products made or derived from tobacco.

In addition, we believe this final rule will help to avoid consumer confusion about which products made or derived from tobacco are intended for a medical use (i.e., as a drug/device) versus for a recreational use. Specifically, FDA wishes to avoid situations where products intended to be sold as tobacco products are marketed with the same claims as products sold as drugs or devices.

D. Comments and Responses Regarding Brown & Williamson and Sottera

(Comment 5) At least one comment agreed with FDA that the Brown & Williamson and Sottera rulings did not define the phrases “as customarily marketed” or “claims of therapeutic benefit,” leaving the Agency with some discretion as to what claims fall within each category when the distinction is not clear under existing precedent.

(Response) FDA agrees that the lack of definitions of the terms “customarily marketed” and “claims of therapeutic benefit” as they apply to products made or derived from tobacco in the relevant case law has created ambiguity and resulted in confusion among regulated industry, which has led FDA to promulgate this rule. Specifically, in the absence of clear judicial direction about what might constitute “claims of therapeutic benefit” and the relationship between tobacco products “as customarily marketed” and the structure/function prong of the drug/device definitions, the Agency believes it is important to clarify its statutory interpretations of the drug/device definitions with respect to products made or derived from tobacco in light of these terms used by the courts.

(Comment 6) Several comments supported FDA’s proposal to treat satisfaction, smoking alternative, and nicotine fix claims as tobacco product claims. However, these comments assert that all products derived from tobacco that lack express therapeutic claims must be regulated as tobacco products. These comments maintained that FDA’s proposed approach--which provides that some structure/function claims will cause products derived from tobacco to be regulated as drugs, devices, or combination products--is inconsistent with the Brown & Williamson and Sottera decisions.

Specifically, the comments argued that neither decision “indicates that ‘customarily marketed’ means anything other than ‘not marketed with therapeutic claims’.” They maintained that the Sottera court “explicitly concluded that the ‘better reading’ of Brown & Williamson was that it deprives FDA of authority to regulate under the FD&C Act any tobacco products marketed ‘without claims of therapeutic effect,’ viewing such products as ‘customarily marketed.’ ” Accordingly, the comments contended that the courts saw only two categories of tobacco products--products marketed with or without therapeutic claims. The comments asked that FDA clarify that it lacks authority to regulate any product made or derived from tobacco as a drug or device absent express therapeutic claims.

(Response) FDA disagrees with these comments and declines to adopt their overly narrow reading of Brown & Williamson and Sottera. First, Brown & Williamson provides no support for the comments’ assertion that therapeutic claims must be express for a product to be subject to FDA’s drug/device jurisdiction. The plaintiffs in Brown & Williamson made this very argument, and the dissenting opinion noted that the FD&C Act “does not use the word ‘claimed’; it uses the word ‘intended’.” See Brown & Williamson, 529 U.S. 120, 170 (2000) (dissenting

opinion). The majority specifically declined to resolve the question. See Brown & Williamson, 529 U.S. 120, 132 (2000).

In addition, as noted in section I.C of the proposed rule, as well as section I.D, neither the Brown & Williamson nor the Sottera decisions defined the term “customarily marketed.” Although the court in Sottera did equate the concept of “therapeutic claims” with the disease prong of the drug and device definitions, there was no such equating of the term “customarily marketed” with the structure/function prong of these definitions. In fact, the term “customarily marketed” itself suggests that the term has some meaning independent of its relationship to the structure/function prong of the drug and device definitions. If the Supreme Court had wanted any structure/function claim to exclude a product made or derived from tobacco from FDA’s drug/device jurisdiction, it could have said so. The structure of section 201(rr) of the FD&C Act, added by the Tobacco Control Act, further supports this interpretation. Following the Supreme Court’s decision in Brown & Williamson, Congress enacted the Tobacco Control Act to give FDA explicit authority to regulate tobacco products. Under section 201(rr)(2), the term “tobacco product” excludes articles that are drugs under section 201(g)(1) and devices under section 201(h) of the FD&C Act. This statutory carve-out includes the structure/function prong of the drug/device definitions.

Having given FDA regulatory authority over tobacco products, if Congress thought that products made or derived from tobacco should never be regulated as drugs or devices under the structure/function prong of the drug or device definitions in the wake of Brown & Williamson, presumably Congress would have written section 201(rr)(2) of the FD&C Act differently. The better reading is that Congress recognized that products made or derived from tobacco as “customarily marketed” would be regulated as tobacco products under the Tobacco Control Act,

but that products made or derived from tobacco meeting the drug/device definitions (including the structure/function prong, to the extent such products were not “customarily marketed”) would continue to be regulated as drugs or devices.

(Comment 7) At least one comment disagreed with some of the examples in the proposed rule of structure/function intended uses that FDA believes remain within its drug/device jurisdiction under the proposal. Specifically, the comment argued that claims about nicotine’s stimulant and weight-loss structure/function effects “remain permissible ‘tobacco product’ claims,” because FDA’s 1996 rulemaking found that stimulant and weight-loss structure/function effects were among the intended uses of cigarettes and smokeless tobacco products (citing 61 FR 44396 at 44630, 44632).

(Response) FDA disagrees with this comment. In the 1996 rulemaking, FDA found that, in addition to causing and sustaining addiction, nicotine in cigarettes and smokeless tobacco causes other psychoactive (mood-altering) effects, including tranquilization and stimulation; and that nicotine in cigarettes and smokeless tobacco controls weight (61 FR 44396 at 44630). The rulemaking further found that these were intended structure/function effects for cigarettes and smokeless tobacco products (id. at 44632). But the central holding of Brown & Williamson was that “customarily marketed” tobacco products were not subject to FDA’s medical product authority, even assuming that such products could be considered to have the intended structure/function effects that FDA attributed to them if their manufacturers and sellers did not claim such effects (529 U.S. at 131-32). As discussed in section I.D, this current rulemaking applies Brown & Williamson, as relevant here, by looking to marketing claims for structure/function effects that were commonly and legally made for “customarily marketed” cigarettes and smokeless tobacco products prior to the date the Brown & Williamson decision

was issued. To the extent the comment read the examples “relieve tension” and “restore mental alertness” as stimulant intended uses, FDA does not believe that they are structure/function intended uses relating to effects of nicotine that were commonly and legally claimed in the marketing of cigarettes and smokeless tobacco products prior to March 21, 2000. Similarly, FDA does not believe that “promotes weight loss” was a “customarily marketed” tobacco product claim within the meaning of Brown & Williamson. Section 1100.5 is written such that, if a particular intended structure/function effect for a product made or derived from tobacco is related to the effects of nicotine commonly and legally claimed prior to March 21, 2000, that product would not be subject to FDA’s drug/device jurisdiction. FDA expects that in some cases this would be a fact-specific, case-by-case inquiry.

Sponsors should also keep in mind that, regardless of whether a product is regulated as a tobacco product or a medical product, the claims made for the product would misbrand the product and subject manufacturers to enforcement action if the claims are false or misleading in any particular, including if the claims are unsubstantiated. Thus, if a particular claim related to the effects of nicotine was used in the marketing of a tobacco product prior to March 21, 2000, but that claim is not substantiated by appropriate evidence, the use of such a claim in current labeling or advertising would likely misbrand the product. In addition, both medical products and tobacco products would be subject to enforcement action under section 201(n) of the FD&C Act if their labeling or advertising fails to reveal facts material in the light of the representations made or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates.

(Comment 8) Several comments argued that the proposed rule was an improper attempt to undermine the court’s holding in Sottera with respect to the regulation of electronic cigarettes.



These comments viewed the proposed rule as an attempt to regulate electronic cigarettes as drugs, and characterized it as an effort to bypass the D.C. Circuit's ruling in Sottera. They also suggested that Sottera made a categorical determination regarding the intended use of electronic cigarettes generally, and maintained that FDA declined to appeal the D.C. Circuit's decision and instead represented that it intended to regulate electronic cigarettes as tobacco products.

(Response) FDA disagrees with these comments. Although the Sottera decision determined that the holding in Brown & Williamson was not limited to cigarettes and smokeless tobacco, the court did not say that electronic cigarettes could never be regulated as drugs or devices. Rather, the court held that FDA can "regulate tobacco products marketed for therapeutic purposes under [the FD&C Act's drug/device provisions]," and observed that "the FDA may establish that NJOY does in fact make therapeutic claims regarding its electronic cigarettes." See Sottera, 627 F.3d at 899. The rule FDA issues here clarifies the circumstances under which a product made or derived from tobacco would be regulated as a drug, device, or combination product, and the circumstances under which it would be regulated as a tobacco product. Manufacturers are free to choose how they would like to market products made or derived from tobacco, but do so in the context of the regulatory framework set forth in the rule.

Moreover, the comments appear to misunderstand the nature of determinations of intended use with respect to FDA-regulated products. As discussed elsewhere in this document, intended use is a case-by-case, fact-specific inquiry in which the Agency may look to any relevant source of evidence, including a variety of direct and circumstantial evidence. See, e.g., Response to Comment 18 in section IV.C. Intended use is not determined on a categorical basis based on product type. Finally, in deciding not to petition for certiorari from the D.C. Circuit's decision in Sottera, FDA did not state or signal that it intended to regulate electronic cigarettes as

tobacco products under all circumstances. Rather, in the wake of the Sottera decision, FDA issued a letter to stakeholders<sup>12</sup>, noting that the Agency would abide by the jurisdictional lines established by Sottera, and was considering issuing a guidance or rulemaking regarding therapeutic claims. This final rule is the result of FDA's consideration of the issues raised by the Sottera decision and clarifies FDA's interpretation of the statutory definitions of drug and medical device with respect to products made or derived from tobacco.

(Comment 9) Several comments asserted that claims that use euphemisms for the delivery of a pharmacologically active dose of nicotine, or state that a tobacco product provides an alternative way of obtaining the effects of nicotine or will provide the same effects as another tobacco product, do not fall within FDA's medical product authority. Four comments took the opposite view. Three of these latter comments remarked that excluding such claims from FDA's medical product authority would authorize manufacturers to continue using claims that were found to be fraudulent and deceptive by the U.S. District Court for the District of Columbia in United States v. Philip Morris USA Inc., 449 F. Supp. 2d 1 (D.D.C. 2006). These comments asserted that claims suggesting a product made or derived from tobacco provides "satisfaction," a "nicotine fix," or "pleasure" are claims about the pharmacological effects of nicotine, and suggested that products bearing such claims should be regulated as medical products. Another comment suggested that FDA treat such claims as evidence of an article's intended use as a drug.

(Response) The Agency disagrees with any suggestion that FDA is authorizing fraudulent claims. The purpose of this rule is to increase clarity regarding the types of intended uses and supporting evidence that make a product made or derived from tobacco subject to

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<sup>12</sup> See <http://www.fda.gov/newsevents/publichealthfocus/ucm252360.htm>.

regulation as a tobacco product versus as a drug, device, or combination product. Regardless of the outcome of that jurisdictional question, the FD&C Act prohibits false and misleading claims in FDA-regulated labeling and advertising (see sections 502(a), 502(n), 502(r), 903(a)(1), and 903(a)(7) (21 U.S.C. 352(a), 352(n), 352(r), 387c(a)(1), and 387c(a)(7)). Similarly, in concluding that certain claims involving “satisfaction,” “pleasure,” “enjoyment,” and “refreshment” are claims about the pharmacological effects of nicotine that were commonly and legally made prior to March 21, 2000, FDA is not authorizing such claims. Rather, the Agency is explaining in more detail its understanding of how the D.C. Circuit’s interpretation of the Tobacco Control Act in Sottera affects the jurisdictional determination. As documented in the annex to the 1996 rule, products made or derived from tobacco were customarily marketed at that time for the pharmacological effects of nicotine, using phrases such as “smoking pleasure” and “satisfaction.”<sup>13</sup> Such terms, as discussed in section II.C, are recognized euphemisms for the delivery of a pharmacologically active dose of nicotine to satisfy addiction--an intended structure/function effect--and were commonly and legally made claims for customarily marketed cigarettes and smokeless tobacco products prior to the date of the Brown & Williamson decision. Thus, FDA continues to believe that Brown & Williamson, as extended and applied to the Tobacco Control Act by Sottera, precludes the Agency from regulating products made or derived from tobacco as medical products on the basis of such claims.

#### E. Comments and Responses Regarding Consumer Confusion

(Comment 10) Comments expressed different opinions about the intended uses of products made or derived from tobacco, primarily e-cigarettes, and whether consumers are able

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<sup>13</sup> See 61 FR 44619 at 44648, August 28, 1996.

to distinguish products that are intended for medical use from products marketed for other uses. Several comments asserted that e-cigarettes are not intended for use as smoking cessation aids, whereas many other comments asserted that e-cigarettes are vital smoking cessation aids. One comment averred that there is no evidence that consumers are confusing e-cigarette products with products that are marketed, labeled, and sold as medical products. Two other comments, however, cited studies that purportedly show many consumers believe e-cigarettes and smokeless tobacco products are effective smoking cessation aids.

(Response) FDA continues to believe that there is consumer confusion about the intended uses of marketed products made or derived from tobacco. Evidence that at least some consumers are confused about the intended uses of products can be found in the comments themselves. We received many comments from individuals who began using e-cigarettes because they believed that e-cigarettes would help them quit smoking. Moreover, as noted in two comments, studies have shown that many consumers are using e-cigarettes to attempt to quit smoking (Ref. 2) despite the fact that no e-cigarette has been approved for use as a smoking cessation aid. We believe that the rule will help to mitigate this confusion and help ensure that consumers do not mistakenly use tobacco products, which are inherently dangerous, for medical uses.

(Comment 11) Several comments expressed concern that this regulation would increase consumer confusion by not allowing ENDS manufacturers to communicate truthful claims to their customers. These comments believed that the regulation would harm, rather than protect public health. Comments also expressed concern that ENDS manufacturers would not be able to state that e-cigarettes could be used for smoking cessation, and ENDS manufacturers would be forced to deceptively market their products. Several comments discussed FDA's authority under

section 911 of the FD&C Act to require premarket authorization of modified risk tobacco products. Some commenters urged FDA to implement section 911 in a manner that does not restrict truthful and non-misleading speech.

(Response) FDA disagrees with concerns that ENDS manufacturers will not be able to make claims that accurately represent their products' intended uses. Manufacturers are free to decide how they would like to market their products, but must meet the appropriate statutory and regulatory standards governing the regulatory pathway they choose. Additionally, the proposed rule would not force e-vapor manufacturers to "deceptively" market their products or risk "being categorized as unapproved medical products and forced off the market." FDA believes that manufacturers of products made or derived from tobacco, including e-vapor manufacturers, could make many types of claims under the rule that would subject them only to tobacco product jurisdiction; the preamble to the proposed rule provides examples of such tobacco product claims, but is not intended to be an exhaustive list. Moreover, section 911 of the FD&C Act allows manufacturers to make truthful and non-misleading modified risk claims with appropriate authorization. Manufacturers that have data to substantiate modified risk claims for a particular product can submit an MRTP application so that FDA can determine whether the product meets the statutory standard and if appropriate, can issue an order authorizing it to be marketed as an MRTP.

FDA continues to believe that smoking cessation claims require close examination. FDA has long considered claims related to smoking cessation in the context of curing or treating nicotine addiction to be evidence of intended uses that confer drug or device jurisdiction. Manufacturers that have data to substantiate cessation claims for a particular product can submit an NDA so that FDA can determine whether the product meets the statutory standard and can

approve the application, if appropriate. The rule's treatment of smoking cessation claims as generally suggestive of a therapeutic purpose means that products marketed with such claims would generally be regulated as medical products. Treating these products as medical products will help assure that such claims are supported by data demonstrating that a product is safe and effective for this intended use. Otherwise, consumers may attempt to quit smoking with unproven products, threatening both individual consumers' health and the public health generally.

(Comment 12) At least one comment suggested that a disclaimer stating that FDA has not approved e-cigarettes for medical use would be sufficient to mitigate any confusion over the intended use of such products. In contrast, several comments argued that disclaimers are insufficient to mitigate any confusion over whether a product made or derived from tobacco is intended for medical use. One of these comments suggested that disclaimers would foster confusion because they often contain statements that conflict with claims that are made elsewhere in the marketing materials and labeling for e-cigarettes and other products.

(Response) FDA does not believe that disclaimers will be sufficient in most cases to mitigate consumer confusion about whether a product made or derived from tobacco is intended for medical use. Studies have shown that disclaimers are frequently ineffective and can actually increase confusion for consumers (Refs. 3 and 4). Thus, where products making claims related to quitting smoking also attempt to disclaim that use in some way, FDA intends to view such disclaimers skeptically.

(Comment 13) Several comments suggested that excluding claims that are euphemisms for the delivery of a pharmacologically active dose of nicotine and those that suggest a tobacco product provides an alternative way of obtaining the effects of nicotine from regulation under the

Agency's drug/device authorities would create consumer confusion because such claims may not be distinguishable from drug or device claims related to the symptoms of nicotine addiction or could be perceived as modified risk claims.

(Response) As stated previously in this section, FDA has determined that the types of claims described in these comments generally do not bring products made or derived from tobacco within its drug and device authority. We acknowledge that there are circumstances in which consumers might be confused by such claims. A consumer might be confused about a product's intended use, for example, if a "satisfying smoking alternative" claim is accompanied by other text or images indicating that the product can help smokers reduce withdrawal symptoms associated with quitting smoking. In that case, the product may be subject to regulation as a drug or device. But as a general matter, FDA does not expect claims that use euphemisms for the delivery of a pharmacologically active dose of nicotine or suggest that a tobacco product provides an alternative way of obtaining the effects of nicotine to cause much confusion. FDA will continue to monitor consumer perception and will take appropriate regulatory action if evidence accumulates showing that consumers are confused by such claims.

#### F. Changes to Existing "Intended Use" Regulations

FDA is also making changes to §§ 201.128 and 801.4. First, the final rule inserts a reference to § 1100.5 to clarify the interplay between these regulations and the final rule. Second, as discussed previously, the Agency does not, absent extraordinary circumstances, regard a firm as intending an unapproved new use for an approved or cleared medical product based solely on that firm's knowledge that the product was being prescribed or used by doctors for such use (see Ref. 1). Accordingly, FDA is taking this opportunity to amend §§ 201.128 and 801.4 to better reflect FDA's interpretation and application of these regulations. These changes

do not reflect a change in FDA's approach regarding evidence of intended use for drugs and devices. These clarifying changes to the intended use regulations apply to drugs and devices generally, and not just to products made or derived from tobacco and intended for human consumption.

### III. Legal Authority

Among the provisions that provide authority for this final rule are sections 201, 503(g), and 701(a) of the FD&C Act (21 U.S.C. 321, 353(g), 371(a)). Section 201 of the FD&C Act defines "drug," "device," and "tobacco product" (subsections (g)(1), (h), and (rr)(1) to (rr)(2)), and section 503(g) of the FD&C Act provides that combination products are those "that constitute a combination of a drug, device, or biological product." Under section 701(a) of the FD&C Act, FDA has authority to issue regulations for the efficient enforcement of the FD&C Act. FDA believes this rule will assist the Agency with efficient enforcement of the FD&C Act because it provides increased clarity to stakeholders, particularly regulated entities, regarding FDA's interpretation of which regulatory framework will apply to particular products and will help consumers differentiate between products that are intended for medical use and products marketed for other uses.

FDA regulates the manufacture, sale, and distribution of drugs, devices, combination products, and tobacco products under the authority of the FD&C Act. Although the regulatory pathways for each product category differ, each product category is subject to similar types of regulatory requirements. For example, FDA's regulatory authority for drugs, devices, combination products, and tobacco products includes authority to review and authorize the marketing of new products as well as to oversee product labeling and advertising. Thus, whether a product meets the definition of a drug, device, or tobacco product under the FD&C Act and this



final regulation, the manufacture, sale, and distribution of the product are subject to the applicable requirements of the FD&C Act.

(Comment 14) At least one comment stated that the proposed rule exceeds FDA's authority.

(Response) FDA disagrees. As described in the proposed rule, FDA has the authority to regulate as a medical product any product that meets the definition of drug, device, or combination product in the FD&C Act, including cigarettes and other tobacco-derived products unless their intended use was the subject of claimed structure/function effects of nicotine commonly and legally claimed in the marketing of cigarettes and smokeless tobacco products prior to March 21, 2000. FDA also has tobacco product jurisdiction over all other products made or derived from tobacco intended for human consumption. The final rule seeks to clarify how products containing nicotine derived from tobacco will be regulated.

#### IV. Description of the Final Rule

##### A. Exclusion From Tobacco Product Regulation (§ 1100.5)

As described in section II, the goal of this final rule is to provide clarity regarding the types of intended uses of products made or derived from tobacco that may fall within the drug/device definitions and therefore cause those products to be regulated as medical products under the FD&C Act. In describing these intended uses, the final rule aims to assist regulated entities in the research and development of products made or derived from tobacco by clarifying which regulatory framework (i.e., the drug/device frameworks or the tobacco framework) will apply to particular products based on their intended use. The final rule is also intended to reduce consumer confusion regarding which products are intended for medical use (i.e., as a drug, device, or combination product) and which may be marketed for recreational or other purposes.

The final rule reflects the legal and regulatory considerations discussed in sections I and II, including the Brown & Williamson and Sottera holdings. Finally, the final rule amends the existing intended use regulations for drugs and devices by inserting in §§ 201.128 and 801.4 a reference to § 1100.5 to clarify the interplay among these regulations and this final rule.

The codified language states the circumstances in which a product made or derived from tobacco would be excluded from the definition of “tobacco product” and be subject to regulation as a drug, device, or combination product. Under the final rule, this exclusion could apply in two circumstances: (1) If the product is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease or (2) if the product is intended to affect the structure or any function of the body in any way that is different from effects related to nicotine that were commonly and legally claimed in the marketing of cigarettes and smokeless tobacco products prior to March 21, 2000.

Conceptually, the codified language follows the disease prong and the structure/function prong (with certain limitations) of the drug and device definitions.

#### 1. Disease Prong

Section 1100.5(a) follows the disease prong. The paragraph elaborates on the statutory language for the disease prong by describing several categories of intended uses that would cause a product made or derived from tobacco to be regulated as a medical product. The categories identified in § 1100.5(a) are not intended to constitute an exhaustive list; nor are these categories necessarily mutually exclusive. In addition, these categories are intended to capture concepts, rather than to suggest that the use (or omission) of particular words is dispositive with respect to FDA’s medical product jurisdiction. These categories are included as examples of types of

intended uses that we believe are particularly relevant for products made or derived from tobacco and that fall within the disease prong.

## 2. Structure/Function Prong

Section 1100.5(b) follows the structure/function prong, but with some changes to reflect the court decisions in Brown & Williamson and Sottera. Specifically, the language in § 1100.5(b) beginning “in any way that is different from...” reflects the fact that, under Brown & Williamson and Sottera, intended structure/function effects related to nicotine will not confer drug/device jurisdiction to the extent they reflect claims that were commonly and legally made for “customarily marketed” tobacco products before the date of the Brown & Williamson decision. This language also references “the marketing of cigarettes and smokeless tobacco products” because these were the product categories considered by the Supreme Court in Brown & Williamson. March 21, 2000, is the date of the Supreme Court’s ruling in Brown & Williamson.

FDA believes that it is important to include a date limitation in § 1100.5(b) to provide greater certainty about the universe of historic structure/function claims the Agency intends to consider when determining whether an intended use of a product made or derived from tobacco is different from effects related to nicotine that were commonly and legally claimed for “customarily marketed” cigarettes and smokeless tobacco products. This bright-line limitation also avoids creating a shifting standard that will cause confusion among consumers and regulated industry. FDA intends to look to the marketing of cigarettes and smokeless tobacco products prior to March 21, 2000, to determine the types of structure/function claims that constitute customary tobacco product marketing. Cigarettes and smokeless tobacco products provide a reasonable proxy for determining how nicotine-related structure/function claims were conveyed

in tobacco product marketing generally. The codified language, however, applies to all products made or derived from tobacco, not just cigarettes and smokeless tobacco.

### 3. Intended Use

As noted in section I.B.2, intended use may be determined from any relevant source and is not based solely on claims made in a product's labeling or advertising materials. For purposes of illustration, however, claims such as "treatment of tobacco dependence," "wean yourself off of nicotine," "for people who wish to quit smoking," "stop smoking aid," "prevent relapse," or "stay quit" generally will bring a product within the intended uses described in § 1100.5(a).<sup>14</sup>

Claims such as "to reduce withdrawal symptoms," "helps reduce symptoms including things like [list of withdrawal symptoms]" and "relieve withdrawal symptoms when you are prohibited from smoking" would be associated with an intended use for relief of nicotine withdrawal symptoms, and would also fall within the intended uses described in § 1100.5(a). Withdrawal symptoms that are medically recognized as relevant to nicotine addiction may be determined by reference to standard classification and diagnostic tools such as the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).

Certain structure/function claims that were not commonly and legally made in the marketing of cigarettes and smokeless tobacco products before March 21, 2000, such as "promotes weight loss," would fall within the intended uses described in § 1100.5(b).

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<sup>14</sup> These and other specific claims mentioned in this document are provided solely as examples. Other claims not mentioned in this document could also reflect an intended use described in the codified language. In addition, as discussed elsewhere in this document, FDA intends to consider the full context of claims for products made or derived from tobacco in making jurisdictional determinations.

In contrast to the examples of medical product intended use claims given in the previous paragraphs, certain other claims made about products made or derived from tobacco would not on their own create an intended use that falls within the codified language.<sup>15</sup> For example, claims such as “smoke free, spit free tobacco pleasure” or “full taste and satisfaction” may be associated with the marketing of tobacco products for refreshment, satisfaction, or enjoyment (which, as discussed in section II.C, are recognized euphemisms for the delivery of a pharmacologically active dose of nicotine to satisfy addiction--an intended structure/function effect--and were commonly and legally made claims for customarily marketed cigarettes and smokeless tobacco products prior to the date of the Brown & Williamson decision). Claims such as “great tasting tobacco satisfaction when you can’t smoke,” “satisfying tobacco alternative,” or “provides the look, feel, and experience of a cigarette” may be associated with the marketing of tobacco products as smoking substitutes. And claims such as “healthier alternative to smoking,” “contains less nicotine than [another product],” or “reduces your risk of lung cancer compared to cigarettes” might be associated with MRTPs, as discussed in section II.A.2.

For products made or derived from tobacco that are intended for investigational use, FDA will consider whether the product is being used in a clinical investigation for an intended use that brings it within the codified language. If it is, the product would meet the definition of “investigational new drug” in § 312.3 (21 CFR 312.3), and the clinical investigation would be subject to the applicable requirements in part 312 (21 CFR part 312).<sup>16</sup> Products made or

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<sup>15</sup> As previously, the specific claims mentioned in this paragraph are provided solely as examples. Other claims not mentioned here could fall outside the intended uses described in § 1100.5.

<sup>16</sup> Note that studies performed to meet statutory requirements in chapter IX of the FD&C Act relating to the impact of tobacco products on cessation behavior are not required to be designed as clinical investigations subject to the investigational new drug application requirements in part 312. Whether a study is considered a clinical investigation of an “investigational new drug” would depend on the study’s design and specific objectives.

derived from tobacco that are intended for investigational use but that do not meet the definition of “investigational new drug” in § 312.3 may be subject to regulation as investigational tobacco products.

B. Existing “Intended Use” Regulations (§§ 201.128 and 801.4)

In the proposed rule, FDA proposed certain changes to FDA’s existing regulations describing the types of evidence that may be considered in determining a medical product’s intended uses (see § 201.128 (drugs), § 801.4 (devices)). These changes were intended to revise the language of the regulations to better reflect how the Agency applies them. As explained in the preamble to the proposed rule, these amendments were intended to clarify FDA’s existing position on intended use, not to change it (80 FR 57756 at 57761). Some comments, however, misunderstood FDA’s proposal, particularly with respect to the proposed deletion of the last sentence of both regulations (§§ 201.128 and 801.4). FDA has now determined that its clarification goals can be better achieved by amending the last sentence of each regulation, rather than deleting them.

Accordingly, the last sentence of § 201.128 is amended to provide that 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), he is required, in accordance with section 502(f) of the FD&C Act, or, as applicable, duly promulgated regulations exempting the drug from the requirements of section 502(f)(1), to provide for the drug adequate labeling that accords with such other intended uses.

Similarly, the last sentence of § 801.4 is amended to provide that if the totality of the evidence establishes that a manufacturer objectively intends that a device introduced into

interstate commerce by him is to be used for conditions, purposes, or uses other than ones for which it has been approved, cleared, granted marketing authorization, or is exempt from premarket notification requirements (if any), he is required, in accordance with section 502(f) of the FD&C Act, or, as applicable, duly promulgated regulations exempting the device from the requirements of section 502(f)(1), to provide for the device adequate labeling that accords with such other intended uses.

As described in the preamble to the proposed rule, FDA's longstanding position is that, in determining a product's intended use, the Agency may look to any relevant source of evidence. This position has solid support in the case law (see, e.g., United States v. Storage Spaces Designated Nos. 8 and 49, 777 F.2d 1363, 1366 (9th Cir. 1985); Action on Smoking and Health v. Harris, 655 F.2d 236, 239 (D.C. Cir. 1980); Nat'l Nutritional Foods Ass'n v. Matthews, 557 F.2d 325, 334 (2d Cir. 1977); United States v. Article of 216 Cartoned Bottles, "Sudden Change," 409 F.2d 734, 739 (2d Cir. 1969); V.E. Irons, Inc. v. United States, 244 F.2d 34, 44 (1st Cir. 1957); Hanson v. United States, 417 F. Supp. 30, 35 (D. Minn.), aff'd, 540 F.2d 947 (8th Cir. 1976)). This position is unchanged.

In the preamble to the proposed rule, FDA also stated "the Agency would not regard a firm as intending an unapproved new use for an approved or cleared medical product based solely on the firm's knowledge that such product was being prescribed or used by doctors for such use" (80 FR 57756 at 57757). Health care providers prescribe or use approved/cleared medical products for unapproved uses when they judge that the unapproved use is medically

appropriate for their individual patients.<sup>17</sup> In these limited circumstances, FDA does not consider a firm's knowledge that a health care provider has used or prescribed its approved/cleared medical product for an unapproved use, by itself, as sufficient to establish the intended use element of a prohibited act related to the lack of premarket approval/clearance of that use or the lack of adequate directions for use.<sup>18</sup> Instead, FDA examines all relevant evidence, which could include, among other facts, a manufacturer's knowledge that health care providers are prescribing or using its approved/cleared medical product for an unapproved use, to determine whether there is sufficient evidence to establish a new intended use.

Before FDA issued the proposed rule, some drug sponsors had expressed concern with the last sentence of § 201.128. That sentence provided, "if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses." (Section 801.4 contains comparable language.) They asserted that, literally read, this sentence would require that, whenever a manufacturer knew that its approved drug was being prescribed for an unapproved use, it would be required to alter the labeling of a drug to provide adequate

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<sup>17</sup> FDA generally does not seek to interfere with the exercise of the professional judgment of health care providers in prescribing or administering, for unapproved uses for individual patients, most legally marketed medical products. This longstanding position has been codified with respect to devices (see 21 U.S.C. 396). While FDA generally does not seek to interfere with the exercise of the professional judgment of veterinarians, certain unapproved uses of drugs in animals are not permitted and result in the drug being deemed unsafe under section 512 of the FD&C Act (see section 512(a)(4) and (5) of the FD&C Act (21 U.S.C. 360b(a)(4) and (5)) and 21 CFR part 530).

<sup>18</sup> See 21 U.S.C. 331(d), 351(f), 352(f)(1), 355(a). That position does not apply to products that are not already legally marketed as medical products for at least one use. Similarly, nothing in this regulation or preamble is intended to impact the application of 21 U.S.C. 333(e), which, subject to limited exceptions, penalizes anyone who "knowingly distributes, or possesses with intent to distribute, human growth hormone for any use in humans other than the treatment of disease or other recognized medical conditions, where such use has been authorized by the Secretary of Health and Human Services under section 505 and pursuant to the order of a physician." Further, Congress or the Agency could promulgate other provisions regarding specific products or classes of medical products that recognize knowledge as sufficient evidence of a particular element of a prohibited act.



directions for an off-label use. They further asserted that this addition to FDA-approved labeling would transform the drug into a new drug that cannot be sold without first obtaining approval of a supplemental new drug application pursuant to 21 U.S.C. 321(p) and 355(a). From this they concluded that, under the last sentence of § 201.128, a manufacturer's mere knowledge of an unapproved use of its approved drug automatically triggers requirements for new labeling that in turn render distribution of that approved product unlawful without approval of a supplemental NDA.

In the proposed rule, the proposed deletion of the last sentence of §§ 201.128 and 801.4 was intended to clarify the following: Where a manufacturer is distributing an approved or cleared medical product, evidence that the manufacturer knows that health care providers are prescribing or using that approved or cleared medical product for an unapproved use would not, by itself, automatically trigger obligations for the manufacturer to provide labeling for the uses for which the health care providers are prescribing or using the product.

FDA's clarification of its position and proposed deletion of the last sentence of these regulations in the proposed rule did not suggest that FDA sought to otherwise narrow the scope of evidence of intended use that FDA may consider. However, some of the comments misunderstood the proposal. For example, some comments asserted--incorrectly--that FDA intended to eliminate manufacturer knowledge altogether as a source of evidence of intended use.

FDA has determined that its clarification goals can be better achieved by amending the last sentence of each regulation, rather than by deleting them. The amended language no longer suggests that a manufacturer's mere knowledge that its approved or cleared product was being prescribed or used for an unapproved use was sufficient to trigger the requirement to provide

adequate labeling. In addition, this amended language provides further clarification by reminding manufacturers that, where the totality of evidence is sufficient to establish a new intended use for a medical product, relevant provisions of the FD&C Act and its implementing regulations will be triggered.

In addition, these amendments reflect FDA's longstanding position, upheld by the courts, that FDA may consider a variety of direct and circumstantial evidence to establish intended use. For example, FDA may also take into account any circumstances surrounding the distribution of the product or the context in which it is sold (see, e.g., United States v. Travia, 180 F. Supp. 2d 115, 119 (D.D.C. 2001)). In the context of medical products, generally, circumstantial evidence often ensures that FDA is able to hold accountable firms that attempt to evade FDA medical product regulation by avoiding making express claims about their products.

#### C. Comments and Responses Regarding Intended Use

(Comment 15) Some comments stated that this clarification of the Agency's interpretation and application of the intended use regulations (§§ 201.128 and 801.4) was helpful because it clarifies a point that has been confusing to industry. Another comment stated that the proposed changes to §§ 201.128 and 801.4 provide less information to manufacturers, not more clarity.

(Response) FDA agrees that clarification was warranted because of the apparent confusion over this point. With this final rule, the Agency is making additional changes to the codified language and providing more explanation to further clarify the meaning of the regulations.

(Comment 16) Some comments asserted that FDA should eliminate another reference to "knowledge" in § 201.128. Before the amendments implemented by this rule, both §§ 201.128

and 801.4 contained the following sentence: “[Intended use] may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.” The comments recommended that FDA delete either the phrase “with the knowledge of such person or their representatives” or the entire sentence from the regulation. At least one comment asserted that its recommended change to delete that phrase is consistent with FDA’s intent in amending the regulations.

(Response) FDA disagrees with these comments. It was not the Agency’s intention to entirely remove manufacturer knowledge from the types of evidence that may be considered in determining a product’s intended use. FDA’s proposed and final rule not only retained this sentence containing the other reference to “knowledge” in the text of both §§ 201.128 and 801.4, but also added “for example” to emphasize that FDA may rely on any relevant source of evidence of intended use. Accordingly, the amended version of this sentence (in both regulations) now reads that “intended use may be shown, for example, by circumstances in which the article is, with the knowledge of such person or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.”

In the context of medical products, generally, varied types of evidence, including evidence of a manufacturer’s knowledge that a product is being used for an unapproved use, often enables FDA to pursue medical product manufacturers who attempt to evade FDA jurisdiction by avoiding express claims with respect to their products. In addition, as courts have recognized, evidence of a manufacturer’s knowledge that a product is being used for an unapproved use can also be used to corroborate other evidence of intended use (see, e.g., United States v. An Article of Device Toftness Radiation Detector, 731 F.2d 1253, 1257 (7th Cir. 1984)

(intended use established in part by witness testimony that device had been used to treat patients, together with other evidence regarding a training program and financial arrangements offered by the defendant).

FDA's intention in proposing to amend §§ 201.128 and 801.4 was more focused than these comments suggest. First, FDA's statement about not relying solely on manufacturer knowledge was limited to approved and cleared products because health care practitioners can generally use and prescribe such products for unapproved uses. That position does not apply to products that are not already legally marketed as medical products for at least one use. Second, manufacturer knowledge may be relevant to intended use, but the Agency would not bring an enforcement action based solely on manufacturer knowledge that an approved/cleared product was being prescribed or used by doctors for an unapproved use. If there is other evidence of intended use, FDA may consider manufacturer knowledge as well as other evidence. Third, FDA proposed deleting, and is now amending, the last sentence of the regulations to avoid the potential misinterpretation that a manufacturer's knowledge of an unapproved use of an approved/cleared medical product, without more, automatically triggers requirements for that manufacturer to provide additional labeling.

(Comment 17) At least one comment suggested that the First Amendment requires the exclusion of knowledge as a category of evidence that may be considered as evidence of intended use.

(Response) FDA disagrees. The First Amendment protects, among other things, freedom of speech, and knowledge and speech are not coextensive. A variety of direct and circumstantial evidence can establish a person's knowledge; a person's speech can be one source--but is not the only source--of evidence of that person's knowledge. Thus, the inclusion

of evidence of knowledge within the types of evidence that may be relevant to establishing intended use does not in itself implicate the First Amendment.

(Comment 18) At least one comment asserted that, under relevant statutory text, legislative history, and case law, evidence of intended use is limited to a manufacturer's promotional claims. Another comment similarly proposed that the Agency focus principally on statements in the product labeling to establish intended use (using advertising material only to a lesser extent). In contrast, still another comment urged FDA to consider manufacturer statements in a variety of contexts, including advertising; press statements; official or unofficial statements made by corporate officials; statements made in social media and other online arenas; and statements made in point-of-sale locations (both traditional retail and online).

(Response) FDA disagrees with the comments urging FDA to narrow the scope of evidence it will consider in determining intended use, and FDA agrees with the comment asserting that evidence relevant to intended use should include a manufacturer's statements in a variety of contexts. Under the former set of comments, FDA could not consider, for example, evidence of a manufacturer's marketing plans or directions to its sales force, evidence of the well-known uses and abuses of its products, and circumstantial evidence relating to the sale and distribution of the product. These comments' suggested narrow view of evidence of intended use would not only create a loophole for manufacturers and distributors to evade FDA oversight of the marketing of approved/cleared medical products for unapproved uses but would also open the door to the marketing of wholly unapproved medical products--all to the detriment of the public health.

As courts have recognized, “[s]elf-serving labels cannot be allowed to mask the vendor’s true intent as indicated by the overall circumstances” (United States v. Storage Spaces

Designated Nos. 8 and 49, 777 F.2d 1363, 1366 n.5 (9th Cir. 1985)). As one court explained, “[a] disease claim made with a wink and a nudge is still a disease claim. To hold otherwise would create an ‘obviously wide loophole’ that would defeat the ‘high purpose of the Act to protect consumers.’” (United States v. Cole, 84 F. Supp. 3d 1159, 1166 (D. Or. 2015) (citation omitted)). Examples of cases where the government has relied on circumstantial evidence to establish intended use include situations where products were labeled as herbal supplements, leather cleaner, incense, potpourri, bath salts, or ‘for research purposes only,’ but in fact contained a pharmacological ingredient such as the active ingredient from approved erectile dysfunction and hair-loss products, albuterol, steroids, or street-drug pharmacological agents (“synthetic marijuana” or “imitation cocaine”). Similar examples for devices include products labeled as laser pointers, massagers, exercise equipment or diving chambers, but actually intended to treat serious conditions such as cancer, HIV, and autism. The government has also considered manufacturers’ directions to their sales forces in determining intended use.

Nothing in the statute requires the narrow scope the comments suggest. As four justices of the Supreme Court recognized in rejecting the arguments reflected in these comments, “The [FD&C Act] ... does not use the word ‘claimed’; it uses the word ‘intended’” (FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 170 (2000) (dissenting opinion) (the majority declined to resolve the issue, *id.* at 131-32)). The language of the regulations is consistent with the statutory framework. As one court recently explained, “[N]owhere does the regulation state that such statements or claims cannot be used to show objective intent unless they were published to the marketplace. To see the absurdity of defendants’ argument, consider a hypothetical in which a medical device manufacturer sells device D, which is approved for use A but frequently prescribed by doctors for off-label use B. If the manufacturer creates a bumper sticker with the

words ‘I intend D to be used for B: Prescribe D for B Today,’ by defendants’ logic that poster is inadmissible evidence of subjective intent so long as it sits in his briefcase, but admissible evidence of objective intent once he sticks it on his car. The Court is not persuaded that there is a legally relevant distinction here; in either scenario, the defendant has manifested into the physical world ‘oral or written statements’ that may be weighed as evidence of objective intent” (United States v. Vascular Solutions, Inc., 181 F. Supp. 3d 342, 347 (W.D. Tex. 2016)).

FDA also disagrees that the case law requires that evidence of intended use be limited to marketing representations by firms, to the exclusion of other types of evidence such as internal firm documents and circumstances surrounding the sale of products. Courts have repeatedly held that intended use is determined by looking to all relevant evidence, including statements and circumstances surrounding the manufacture and distribution of a medical product (see, e.g., United States v. Article of 216 Cartoned Bottles, “Sudden Change,” 409 F.2d 734, 739 (2d Cir. 1969) (“It is well settled that the intended use of a product may be determined from its label, accompanying labeling, promotional material, advertising and any other relevant source.”) (citations omitted); V.E. Irons, Inc. v. United States, 244 F.2d 34, 44 (1st Cir. 1957) (observing that a court is “free to look to all relevant sources in order to ascertain what is the ‘intended use’ of a drug”)). As explained by one court: “Whether a product’s intended use makes it a device depends, in part, on the manufacturer’s objective intent in promoting and selling the product. All of the circumstances surrounding the promotion and sale of the product constitute the ‘intent’. It is not enough for the manufacturer to merely say that he or she did not ‘intend’ to sell a particular product as a device. Rather, the actual circumstances surrounding the product’s sale ... determine the ‘intended’ use of the product as a device under the Act” (United States v. 789

Cases, More or Less, of Latex Surgeons' Gloves, 799 F. Supp. 1275, 1285 (D. Puerto Rico 1992) (emphasis in original) (internal citations omitted)).

Indeed, courts have rejected the comments' proposition that evidence of intended use is limited to a manufacturer's public claims concerning a device or drug (see Nat'l Nutritional Foods Ass'n v. Matthews, 557 F.2d 325, 334 (2d Cir. 1977) ("In determining whether an article is a 'drug' because of an intended therapeutic use, the FDA is not bound by the manufacturer's subjective claims of intent but can find actual therapeutic intent on the basis of objective evidence. Such intent also may be derived or inferred from labeling, promotional material, advertising, and any other relevant source.") (internal citation and quotations omitted); United States v. Travia, 180 F. Supp. 2d 115, 119 (D.D.C. 2001) ("Labeling is not exclusive evidence of the sellers' intent. Rather, as the very language quoted by the defendants themselves states, 'it is well established 'that the intended use of a product, within the meaning of the [FD&C Act], is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source' ... even consumer intent could be relevant, so long as it was pertinent to demonstrating the seller's intent ... [I]f the government's allegations are true, the sellers did not need to label or advertise their product, as the environment provided the necessary information between buyer and seller. In this context, therefore, the fact that there was no labeling may actually bolster the evidence of an intent to sell a mind-altering article without a prescription-- that is, a misbranded drug.") (citations omitted); United States v. Vascular Solutions, Inc., 181 F. Supp. 3d 342, 347 (W.D. Tex. 2016) ("Even were this Court at liberty to depart from the Fifth Circuit's position, however, it would still deny defendants' motion; though [21 CFR] § 801.4 indeed says that 'objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives,' nowhere does the



regulation state that such statements or claims cannot be used to show objective intent unless they were published to the marketplace.”); see also United States v. Storage Spaces Designated Nos. 8 and 49, 777 F.2d 1363, 1366 n.5 (9th Cir. 1985) (concluding that products innocuously labeled as “incense” and “not for drug use” were in fact drugs where the “overall circumstances” demonstrated vendor’s intent that products be used as cocaine substitutes); United States v. An Article of Device Toftness Radiation Detector, 731 F.2d 1253, 1257 (7th Cir. 1984) (intended use established in part by witness testimony that device had been used to treat patients, together with other evidence regarding a training program and financial arrangements offered by the defendant); United States v. Undetermined Quantities of an Article of Drug Labeled as “Exachol”, 716 F. Supp. 787, 791 (S.D.N.Y. 1989) (explaining that “FDA is not bound by the vendor’s subjective claims of intent” and that “[a]n article intended to be used as a drug will be regulated as a drug ... even if the products labeling states that it is not a drug”).

(Comment 19) At least two comments asserted that FDA should significantly contract its proposed definitions of “intended uses” because the First Amendment protects truthful speech. One comment stated that, under Central Hudson Gas and Electric Corp. v. Public Services Commission, 447 U.S. 557, 566 (1980), government regulation of truthful speech concerning a lawful activity violates the First Amendment unless government regulators can establish that: (1) They have identified a substantial government interest; (2) the regulation directly advances that asserted interest; and (3) the regulation is no more extensive than is necessary to serve that interest. The comment then argued that a complete prohibition of truthful speech by manufacturers and their representatives concerning the off-label uses of a drug or device does not satisfy this test.

Similarly, another comment urged FDA to confirm that truthful and non-misleading speech cannot form the basis of a manufacturer's intended use of a medical product. That comment asserted that courts have recently held that enforcement actions based on truthful, non-misleading speech to health care professionals violates core First Amendment values, citing United States v. Caronia, 703 F.3d 149 (2d Cir. 2012) and Amarin Pharma, Inc. v. FDA, 119 F. Supp. 3d 196 (S.D.N.Y. 2015).

(Response) FDA is separately examining its rules and policies relating to firm communications regarding unapproved uses of approved/cleared medical products, with the goal of determining how best to integrate the significant and sometimes competing public health and safety interests served by FDA's regulatory approach related to unapproved uses of medical products with ongoing developments in science and technology, medicine, health care delivery, and constitutional law. To that end, FDA held a two-day public hearing on November 9 and 10, 2016, to obtain input on these issues, and created a docket for the submission of written comments (see, e.g., 81 FR 60299, Sept 1, 2016, announcing a public hearing and request for comments on Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products, available at:

<http://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm489499.htm>). That examination is ongoing. In contrast, the purpose of amending §§ 201.128 and 801.4 in this rulemaking is to clarify the scope of these regulations in response to assertions by industry that they did not understand the meaning of the regulations in their previous form.

The broader policy questions and the related First Amendment issues are thus being considered in a separate proceeding. Nevertheless, it is important to note here that we do not agree with the assertion that the current case law allows FDA to consider speech as evidence of

intended use only when it is false or misleading. Courts have held that the government's reliance on speech as evidence of intended use under the FD&C Act does not infringe the right of free speech under the First Amendment based on Supreme Court precedent establishing that "[t]he First Amendment . . . does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent" (Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993)). The D.C. Circuit applied that precedent in the context of the FD&C Act and held that "th[e] use of speech to infer intent, which in turn renders an otherwise permissible act unlawful, is constitutionally valid" and hence "it is constitutionally permissible for the FDA to use speech [by the manufacturer] . . . to infer intent for purposes of determining that [the manufacturer's] proposed sale . . . would constitute the forbidden sale of an unapproved drug" (Whitaker v. Thompson, 353 F.3d 947, 953 (D.C. Cir. 2004); see also Flytenow, Inc. v. FAA, 808 F.3d 882, 894 (D.C. Cir. 2015) (upholding "us[e of] speech (postings on Flytenow.com) as evidence that pilots are offering service that exceeds the limits of their certifications")). Courts applying that reasoning have found that the government's reliance on speech as evidence of intended use under the FD&C Act does not infringe the right of free speech under the First Amendment (see United States v. Lebeau, 654 Fed. App'x 826, 830-31 (7th Cir. 2016) (per curiam), petition for cert. filed, NO. 16-7125 (U.S. Oct. 13, 2016); Whitaker v. Thompson, 353 F.3d 947, 953 (D.C. Cir. 2004); United States v. Article of Drug Designated B-Complex Cholinol Capsules, 362 F.2d 923, 927 (3d Cir. 1966); United States v. Cole, 84 F. Supp. 3d 1159, 1166 (D. Or. 2015); United States v. Regenerative Sciences, LLC, 878 F. Supp. 2d 248, 255-56 (D.D.C. 2012), aff'd, 741 F.3d 1314 (D.C. Cir. 2014); United States v. Livdahl, 459 F. Supp. 2d 1255, 1268 (S.D. Fla. 2005); United States v. Lane Labs-USA, Inc., 324 F. Supp. 2d 547, 579-80 (D.N.J. 2004); United States v. General Nutrition, Inc., 638 F. Supp. 556, 562 (W.D.N.Y. 1986); see also Spectrum

Pharms., Inc. v. Burwell, 824 F.3d 1062 (D.C. Cir. 2016) (manufacturer promotion of a generic drug for use approved for the sponsor but not for the generic may lead to enforcement action for misbranding)).

Although the district court in Amarin Pharma, Inc. v. FDA held that the Caronia decision foreclosed reliance (in the Second Circuit) on this doctrine in the context of an FDA enforcement action where the misbranding was based solely on truthful, non-misleading speech regarding the unapproved use of an approved drug, the Second Circuit has more recently confirmed that “Caronia left open the government's ability to prove misbranding on a theory that promotional speech provides evidence that a drug is intended for a use that is not included on the drug's FDA-approved label” (United States ex rel. Polansky v. Pfizer, Inc., 822 F.3d 613 n.2 (2d Cir. 2016)).

In addition, FDA's consideration of speech as evidence of intended use under its statutory and regulatory framework advances substantial public health interests relevant to analyses under Central Hudson Gas & Electric Corp. v. Public Service Comm'n, 447 U.S. 557, 563-64 (1980). The medical products FDA regulates have the potential to adversely impact public health and safety. Congress specifically developed the premarket review frameworks for medical products in response to public health tragedies<sup>19</sup> and after determining that: (1) Exclusive reliance on postmarket remedies, such as enforcement actions for false or misleading labeling, is

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<sup>19</sup> The Federal Food, Drug, and Cosmetic Act of 1938, which introduced the requirement that firms demonstrate a drug product to be safe before being marketed, followed the deaths of approximately 100 people from ingesting “Elixir Sulfanilamide,” in which the lethal substance diethylene glycol was used as a solvent. Prior to 1938, there were no premarket requirements that mandated that the firm test its product's safety. The passage of the 1962 drug amendments was precipitated in part by the distribution of thalidomide, a sleeping pill that caused birth defects when taken by pregnant women. See W. F. Janssen article (Ref. 20). Significant problems with medical devices likewise preceded the Medical Device Amendments of 1976, including significant defects in cardiac pacemakers that led to 34 voluntary recalls involving 23,000 units, and serious side effects following implantation of intraocular lenses, including serious impairment of vision and the need to remove the eyes of some patients (H.R. Rep. No. 94-853, at 8 (1976)).

unacceptable as a public health strategy for medical products because it does not sufficiently prevent harm and injury to patients and (2) safety and effectiveness must be evaluated for each marketed intended use of a medical product to prevent the harm that occurs when patients are prescribed or use ineffective treatments and to ensure that the benefits of an intended use outweigh its risks. The premarket review requirements of the FD&C Act and the Public Health Service Act provide mechanisms to help ensure that protections are in place that will allow the public to obtain the benefits of these products while mitigating the risks. More specifically, FDA's statutory authorities, regulations, and implementation policies advance substantial public health interests including: Motivating the development of robust scientific data on safety and efficacy;<sup>20</sup> maintaining the premarket review process for safety and efficacy of each intended use in order to prevent harm, protect against fraud, misrepresentation, and bias, and prevent the diversion of healthcare resources toward ineffective treatments;<sup>21</sup> ensuring required labeling is

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<sup>20</sup> See R. Eisenberg article (Ref. 11) (“By requiring that firms conduct rigorous clinical trials before bringing their products to market and before making promotional claims for their products, the FDA plays an important structural role in promoting a valuable form of biomedical R&D that private firms are undermotivated to perform on their own.”); A. Kesselheim and M. Mello article (Ref. 12) (“There [would] be no need for companies to design these studies to meet the FDA’s standards for methodological rigor if the companies have no intention of submitting an application for approval of the new use but rather intend to use the study findings only in marketing communications. Companies [could] design studies in ways that maximize the chances of obtaining a desired result and select which studies to emphasize in promotional communications, ignoring others that do not support their promotional message.”); R. Stafford article (Ref. 13) (Encouraging unapproved uses “undermines the incentives for manufacturers to perform rigorous studies--and instead subtly encourages them to game the system by seeking approval for secondary indications for which clinical trials are less complicated and less expensive. And off-label use may discourage evidence-based practice.”).

<sup>21</sup> See, e.g., S. Kesselheim and J. Avorn article (Ref. 5) (“In the pharmaceutical market, determining whether a drug is safe and effective for an intended use can involve dozens of FDA scientists poring over extensive databases of studies in animals, toxicologic evaluations, and clinical trials. In essence, the agency acts as a learned intermediary on behalf of prescribing physicians.”); C. Good and W. Gellad article (Ref. 6) (“Even in situations where an off-label indication has been studied, pharmacokinetics, drug-disease interactions, and other safety considerations are unlikely to have been studied systematically to the level required during the FDA drug approval process. Likewise, few clinicians have the time or the motivation to review evidence for those off-label indications to arrive at a balanced assessment of the risks and benefits to support the appropriate use of that drug”); T. Eguale et al. article (Ref. 7) (summarizing study across cohort of 46,000 patients, and concluding that unapproved use of prescription drugs is associated with adverse drug events, particularly where those uses lack strong scientific evidence in the form of at least one randomized controlled trial).

accurate and informative; protecting the integrity and reliability of promotional information regarding medical product uses; protecting human subjects receiving experimental treatments; ensuring informed consent; maintaining incentives for clinical trial participation; protecting innovation incentives, including statutory grants of exclusivity; and promoting the development of products for underserved patients.

At the same time, health care providers also prescribe and use approved/cleared medical products for unapproved uses when they judge that the unapproved use is medically appropriate for their individual patients. Scientific or medical information regarding unapproved uses of products may in some cases help health care providers make better decisions regarding patients, such as where the patient has a disease for which there is no approved/cleared treatment, where the patient is part of a population that has not been studied, or where all approved/cleared treatments have been exhausted. However, in other cases, the use of approved/cleared medical products for unapproved uses has also been associated with significant harm to patients, fraud, and waste of health care resources.<sup>22</sup>

FDA's current implementation approach seeks to integrate the complex mix of numerous and sometimes competing interests at play while also taking into account First Amendment issues. For example, FDA has issued guidance documents to describe some of the circumstances when it would not consider a firm's distribution of reprints, clinical practice guidelines, or reference texts regarding unapproved uses of approved/cleared medical products to be evidence

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<sup>22</sup> See J. Avorn et al. article (Ref. 8) ("Considerable research shows that marketing can drive prescribing practices, which in turn can lead to adverse patient outcomes if those decisions are not evidence-based."); A. Kapczynski article (Ref. 9) ("To be effective, a company's marketing must also influence the prescribing patterns of physicians. ... [T]here is a strong and specific association between pharmaceutical marketing and physician behavior, independent of the evidence supporting the products."); R. Cardarelli et al. article (Ref. 10) (pharmaceutical industry marketing to prescribing physician creates the potential for prescribing practices that may not benefit the patient, which contribute to escalating health care costs); T. Egualle et al. article (Ref. 7).

of intended use; and issued a draft guidance on unsolicited requests, confirming FDA's longstanding position that it would not consider a firm's providing truthful, balanced, non-misleading, and non-promotional scientific or medical information (including information about an unapproved use) that is responsive to unsolicited requests for information about FDA-regulated medical products to be evidence of intended use. FDA takes the same view of firms' presenting truthful and non-misleading scientific information about unapproved uses at medical or scientific conferences when done in non-promotional settings and not accompanied by promotional materials.

There are several points worth noting regarding the Central Hudson evaluation conducted by Second Circuit panel majority in United States v. Caronia. First, the panel majority's analysis was limited to addressing the constitutionality of a specific "construction of the FDCA's misbranding provisions to prohibit and criminalize off-label promotion" (see 703 F.3d 149, 161-64, 166-69 (2d Cir. 2012)). The Caronia majority did not conduct a Central Hudson evaluation of FDA's actual approach to manufacturer communications regarding unapproved uses of approved medical products, as described in the preceding paragraph. Second, the panel majority did not consider the multiple facets of public health advanced by FDA's statutory authorities, regulations, and implementation policies, which include motivating the development of reliable scientific evidence that enables the evaluation of the safety and effectiveness of each intended use of a medical product; maintaining the premarket review process for safety and efficacy of each intended use in order to prevent harm, protect against fraud, misrepresentation, and bias, and prevent the diversion of healthcare resources toward ineffective treatments; ensuring required labeling is accurate and informative; protecting the integrity and reliability of promotional information regarding medical product uses; protecting human subjects receiving

experimental treatments; ensuring informed consent; maintaining incentives for clinical trial participation; protecting innovation incentives, including statutory grants of exclusivity; and promoting the development of products for underserved patients. The court’s limited review of the interests at stake necessarily affected the rest of its Central Hudson analysis. Furthermore, the results of an exceptionally large Canadian study showing an association between unapproved uses and adverse drug events<sup>23</sup> were released more than three years after the Caronia decision. Accordingly, the Caronia court, in conducting its Central Hudson evaluation, did not have the benefit of considering the significant findings of this study.

(Comment 20) Several comments asserted that FDA should take this opportunity to bring other related regulations and guidance documents into conformance with modern First Amendment case law. These comments suggested, for example, that FDA reconsider its approach to substantial evidence to support manufacturer communications to health care professionals about approved drugs, reconsider its interpretation of the term labeling, and revise its regulations to confirm that FDA will abide by restrictions on FDA authority imposed by federal courts in United States v. Caronia, 703 F.3d 149 (2d Cir. 2012), and similar First Amendment decisions. At least one comment asserted, citing United States v. Caronia, that FDA’s interpretation and implementation of the FD&C Act restricts speech based on the identity of the speaker. The comment further asserted that any restrictions on truthful and non-misleading speech are subject to “heightened judicial scrutiny” and are “presumptively invalid” under Sorrell v. IMS Health Inc., 564 U.S. 552, 565, 571 (2011), Reed v. Town of Gilbert, 135 S. Ct. 2218, 2226 (2015), and Rosenberger v. Rector & Visitors of the Univ. of Va., 515 U.S.

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<sup>23</sup> T. Eguale et al. article (Ref. 7) (as noted above, summarizing study across cohort of 46,000 patients, and concluding that unapproved use of prescription drugs is associated with adverse drug events, particularly where those uses lack strong scientific evidence in the form of at least one randomized controlled trial).



819, 828 (1995). Another comment, quoting Bolger v. Youngs Drug Prods., 463 U.S. 60, 66 (1983), asserted that FDA should recognize that commercial speech is limited to speech that “does no more than propose a commercial transaction.” Another comment urged FDA to open a separate docket related to free speech issues regarding medical products.

(Response) To the extent these comments propose that FDA consider, in this rulemaking, issues that are beyond the scope of this rulemaking, FDA declines the suggestion. FDA agrees with the comment that suggests that broader First Amendment issues should be considered in the context of separate proceedings. FDA notes that there are separate proceedings that are currently ongoing (see, e.g., 81 FR 60299, Sept 1, 2016, announcing a public hearing and request for comments on Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products, available at:

<http://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm489499.htm>).

In addition, FDA notes its disagreement with certain characterizations of the existing case law. First, as discussed earlier, the court in Caronia based its analysis on a legal theory that is more proscriptive than the one FDA actually holds. Second, the cited Supreme Court cases did not overrule the Central Hudson test for commercial speech. The Supreme Court in Sorrell confirmed that, where, as here, the speech in question is commercial, the Court applies the “commercial speech inquiry” as outlined in Central Hudson (Sorrell v. IMS Health Inc., 564 U.S. 552, 571-72 (2011); see also 1-800-411-Pain Referral Service, LLC v. Otto, 744 F.3d 1045, 1055 (8th Cir. 2014) (observing that Sorrell held that content- or speaker-based restrictions on commercial speech are subject to “heightened scrutiny,” and using the Central Hudson test to determine the constitutionality of such restrictions)). The Sorrell Court also confirmed that

“content-based restrictions on protected expression are sometimes permissible, and that principle applies to commercial speech” (Sorrell, 564 U.S. at 579).

In Reed v. Town of Gilbert, the Court applied strict scrutiny to content-based restrictions on non-commercial speech in public fora. That holding has no bearing on the commercial speech at issue here (see, e.g., Sarver v. Chartier, 813 F.3d 891, 903 n.5 (9th Cir. 2016) (stating that Reed does not apply to laws governing commercial speech); Mass. Ass’n of Private Career Sch. v. Healey, 159 F. Supp. 3d 173, 192-93 (D. Mass. 2016) (same); San Francisco Apt. Ass’n v. City & Cnty. of San Francisco, 142 F. Supp. 3d 910, 922 (N.D. Cal. 2015) (same), appeal docketed, No. 15-17381 (9th Cir. Dec. 3, 2015). The Supreme Court’s 1995 decision, Rosenberger v. Rector & Visitors of the Univ. of Va., 515 U.S. 819, likewise did not involve commercial speech.

Third, we disagree with the one comment that asserts, quoting Bolger v. Youngs Drug Prods., 463 U.S. 60, 66 (1983), that the Supreme Court limited the application of the Central Hudson test to speech that literally “does no more than propose a commercial transaction.” Although the Court in Bolger referred to speech that proposes a commercial transaction as “the core notion of commercial speech,” the Court then explained that “informational pamphlets” that “cannot be characterized merely as proposals to engage in commercial transactions” were nevertheless commercial speech based on a combination of relevant circumstances, such as mentioning the seller’s product in the pamphlet and the economic motivation of the seller (see Bolger, 463 U.S. at 66-68 (emphasis added); see also Conn. Bar Ass’n v. United States, 620 F.3d 81, 93-94 (2d Cir. 2010)).

(Comment 21) Several comments suggested that FDA replace the phrase “is intended for use” in the first sentence of § 1100.5 with other phrases, such as “is commonly used” or “is primarily used.”

(Response) FDA declines this suggestion. The phrase “is intended for use” is necessary because it reflects the fact that FDA’s regulatory authority over a product made or derived from tobacco is, in the context of regulating them as medical products, dependent upon the product’s intended use.

(Comment 22) Several comments urged FDA not to consider a manufacturer’s knowledge when determining a manufacturer’s intent with respect to the regulation of human cells, tissues, and cellular and tissue-based products (HCT/Ps). The comments also request that the Agency use notice and comment rulemaking instead of guidance to make changes regarding manufacturer intent related to HCT/Ps.

(Response) These comments concern regulations and guidance documents relating specifically to HCT/Ps and are outside the scope of this rulemaking.

#### D. Comments and Responses Regarding Marketing Concerns

(Comment 23) At least one comment suggested that FDA amend § 1100.5(a) to incorporate the following points: (1) Products intended for use in the cure and treatment of smoking or any other tobacco product use are subject to regulation as medical products; (2) products intended for use for the prevention of relapse into any smoking, tobacco product, or nicotine relapse are subject to regulation as medical products; and (3) relief from nicotine withdrawal symptoms also includes relief from smoking or tobacco use withdrawal symptoms.

(Response) FDA agrees that the three uses identified in the comment appear to be intended uses that would render the products subject to regulation as medical products. Section

1100.5(a) explains that a product made or derived from tobacco is subject to regulation as a medical product if it is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease. For illustrative purposes, the section also provides several examples of intended uses that will subject a product to regulation as a medical product. We believe the list of examples, which is not intended to be exhaustive, adequately illustrates the types of intended uses that will subject a product made or derived from tobacco to regulation as a medical product. Thus, while we agree that the three identified uses appear to be intended uses that would render the products subject to regulation as medical products, we decline to amend the list to incorporate the uses identified by the comment.

(Comment 24) At least one comment objected that the rule would limit e-cigarettes to marketing claims of “smoking pleasure” and “smoking satisfaction” since that is how traditional tobacco products were “customarily marketed” prior to March 21, 2000. The comment asserted that the rule would either force e-cigarettes off the market as unapproved medical products, or require e-cigarettes to be marketed similar to how traditional tobacco products were marketed prior to March 21, 2000, which would be deceptive because e-cigarettes are not intended for smoking pleasure or tobacco satisfaction. The comment argued that FDA should treat e-cigarettes differently from products that both contain tobacco leaf and were commercially available before March 21, 2000, when considering the types of claims that will subject a product made or derived from tobacco to regulation as a medical product.

(Response) FDA disagrees. As explained elsewhere in this document, we believe that the rule gives manufacturers and retailers ample flexibility to market e-cigarettes in a manner that is distinct from how cigarettes were marketed prior to March 21, 2000. The date of March 21, 2000, is relevant only to considering claims about a product’s effects related to nicotine on the

structure or function of the body as evidence of a product's intended use. E-cigarette manufacturers' and retailers' claims related to customizability, number of puffs per cartridge or charge, and various other differentiating features that do not relate to nicotine structure/function effects, irrespective of whether such claims were customarily and legally made in the marketing of cigarettes and smokeless tobacco products before March 21, 2000, should generally not affect the determination of a product's intended use. A manufacturer's making a modified risk claim for a specific tobacco product renders the product an MRTP, which can be marketed only after the manufacturer substantiates any modified risk claims in an MRTP application and after FDA determines that the product meets the statutory standard. Additionally, if a manufacturer intends that its product be used for cessation, it can submit an NDA, Abbreviated New Drug Application (ANDA), Premarket Approval Application (PMA), or premarket notification submission so that FDA can determine whether the product meets the statutory standard and can approve the application or clear the submission, if appropriate.

(Comment 25) At least one comment questioned whether the marketing for tobacco products that are not MRTPs may contain useful contextual information (e.g., ingredient information).

(Response) This comment is outside the scope of this rulemaking because it does not relate to the circumstances in which a product that is made or derived from tobacco will be regulated as a medical product or a tobacco product.

(Comment 26) Several comments stated that ENDS manufacturers need to be able to inform and explain how to properly use vaping devices to help novices to prevent them from having accidents. The comments stated that vape shops need to be able to correctly educate consumers on how to use the products they sell.

(Response) FDA agrees. FDA recognizes that manufacturers may wish to provide instructions to consumers on how to use novel tobacco products, and instructions may be helpful in some cases in preventing consumer injury, such as nicotine poisoning or injuries from exploding batteries. Manufacturers may provide instructions to the consumer in many ways, including verbal instruction. However, if the instructions provided by the manufacturer convey that the product is to be used as a cessation device, then the product will generally be regulated as a medical product. Additionally, if the instructions make a modified risk claim, then the manufacturer must submit an MRTP application so that FDA can determine whether the product meets the statutory standard and can issue an order authorizing it to be marketed as an MRTP.

(Comment 27) Several commenters noted that tobacco products are advertised in a variety of media, including traditional print or mainstream media, blogs, social media, testimonials, and links to studies or media reports on Web sites. One comment observed that manufacturers of ENDS products often use online blogs as a way to make implicit or explicit cessation claims, and in some cases such assertions run counter to disclaimers posted on the same Web site that hosts the blog. Another comment noted that manufacturers used consumer testimonials that make cessation or MRTP claims on their company Web sites. Commenters observed that conflicting claims in advertising caused confusion among consumers regarding whether ENDS products are FDA-approved smoking cessation aids.

(Response) FDA agrees. Tobacco products are advertised in a variety of media, and advertisements may include conflicting information regarding whether the product is a recreational tobacco product or an FDA-approved smoking cessation product. When conflicting claims are made to the consumer, consumers can be confused by those claims. Thus, FDA believes that manufacturers' making smoking cessation claims for any product creates a strong

suggestion of therapeutic benefit to the user that would subject the product to regulation under FDA's medical products authority. Such a suggestion generally will be difficult to overcome absent clear context indicating that the product is not intended for use to cure or treat nicotine addiction or its symptoms, or for another therapeutic purpose. As discussed in response to Comment 12, where products making claims related to quitting smoking also attempt to disclaim that use in some way, FDA intends to view such disclaimers skeptically because of the likelihood of consumer confusion. In most cases, FDA does not believe that disclaimers will sufficiently mitigate consumer confusion related to the intended therapeutic use of the product.

(Comment 28) Several comments stated that adolescent smokers are especially vulnerable to cessation and therapeutic claims in tobacco product marketing. These comments believe that adolescents misperceive the supposed benefits and underestimate the relative harms, risks, and addictive properties of e-cigarettes and other non-cigarette products.

(Response) FDA agrees that youth and young adults generally "underestimate the tenacity of nicotine addiction and overestimate their ability to stop smoking when they choose" (Ref. 14). For example, one survey found that "nearly 60 percent of adolescents believed that they could smoke for a few years and then quit" (Ref. 15). FDA also believes that unsubstantiated cessation claims that reach adolescents may confuse teens and lead teens to believe that these products are FDA-approved smoking cessation products. For example, a teenager in a recent qualitative study said, "I heard that the only reason they were made is to help people get off from cigarettes for people that want to quit. You would use an e-cigarette to help you quit supposedly. It was on the news" (Ref. 16). FDA believes it is important to avoid consumer confusion about which products are intended for medical uses versus recreational or other tobacco product uses among both adolescents and adults, and this rule will help consumers.

(Comment 29) At least one comment stated that users consider ENDS and smokeless tobacco products effective cessation interventions. The comment believed that many people use these products to try to stop smoking because they are influenced by manufacturers' and sellers' marketing messages that make cessation and therapeutic claims about ENDS and other non-cigarette tobacco products.

(Response) FDA agrees that marketing can influence how consumers perceive tobacco products, and products advertised with cessation claims can lead consumers to believe that the product is an FDA-approved smoking cessation device. FDA also agrees that many consumers are using ENDS products for therapeutic purposes. One study concluded that, among State tobacco cessation quitline callers, the most common reported reason for using e-cigarettes was to cut down on, or quit, traditional tobacco use (Ref. 17). Another study concluded that some smokers who were interested in quitting were using ENDS for cessation purposes, possibly discouraging the use of proven smoking cessation treatments, delaying cessation, and thus prolonging exposure to harmful agents in combusted tobacco as an unintended consequence. Additionally, FDA received a large number of comments from individuals using ENDS for therapeutic purposes. One purpose of this regulation is to avoid consumer confusion about which products made or derived from tobacco are intended for a medical use versus for a recreational use.

#### E. Other Comments and Responses

(Comment 30) At least one comment expressed concern that since the Sottera decision, FDA has not taken action against products made or derived from tobacco and making claims that were "clearly therapeutic." In order to protect consumers from "false, misleading, and confusing tobacco industry claims," the comment asks that products made or derived from tobacco making



claims without an MRTP order be regulated as drug/device products in the Center for Drug Evaluation and Research.

(Response) FDA disagrees with the comment to the extent that the comment suggests that tobacco products properly regulated as MRTPs be regulated as drugs or devices in the absence of an MRTP order. Tobacco products making modified risk claims are regulated under the tobacco product authorities in the FD&C Act, and an MRTP marketed without an MRTP order would be subject to enforcement as a tobacco product, rather than subject to regulation as a drug or medical device product. With respect to enforcement generally, FDA notes that it is issuing this rule to clarify its interpretation of the drug and device definitions with respect to products made or derived from tobacco, and that it expects this clarification to assist industry in determining the applicable regulatory framework for particular products and help consumers differentiate between products that are intended for medical use and products intended for other uses.

(Comment 31) At least one comment observed that researchers may wish to study the effects that a product made or derived from tobacco has on health outcomes (e.g., withdrawal symptoms, hypertension, etc.) or on the structure and function of the body (e.g., blood pressure, lung function), or the effects of substituting one product made or derived from tobacco for another product. The comment asserted that the methods and measures of such studies are not evidence that the product being investigated is a drug and that FDA should not require an investigational new drug application (IND) for these studies unless they are sponsored by a manufacturer with the intention of supporting a health or medical drug claim.

(Response) The regulations in part 312 set forth the circumstances in which an IND is required for clinical investigations in which a drug is administered to human subjects. The IND

requirement applies irrespective of whether the investigation is sponsored by a manufacturer or an academic institution. A study involving a product made or derived from tobacco will generally require an IND if the product, as used in the study, is subject to regulation as a drug. Whether the product, as used in the study, is subject to regulation as a drug depends on whether the product is being investigated for any of the purposes described in § 1100.5(a) or (b) of this rule. To determine if a product made or derived from tobacco is being investigated for one of these purposes, FDA generally would review the protocol for the study, including the proposed methods and measures. In the Agency's experience, the proposed methods and measures for a study can provide insight into the purposes for which a product is being investigated. Ultimately, however, whether a product is being investigated for a therapeutic purpose, and thus whether the study requires an IND, is a fact-specific, case-by-case inquiry. Additional information about the IND requirement can be found in the FDA guidance document entitled "Investigational New Drug Applications (INDs)--Determining Whether Human Research Studies Can Be Conducted Without an IND." We encourage researchers to review this guidance document, which is available on FDA's Web site at <http://www.fda.gov/downloads/UCM229175.pdf>.

(Comment 32) At least one comment encouraged FDA to coordinate between centers to promote development of safer tobacco products as well as more effective medical products for the treatment of nicotine addiction. This comment also argued that FDA should not allow similar or identical products to be marketed as both tobacco products and medical products, and should consider approving categories of products, rather than individual products, for smoking cessation. This comment also expressed concern about dual use between tobacco product categories.

(Response) FDA agrees with this comment to the extent the comment considers the proposed rule to promote effective coordination between centers by clarifying which center should take the lead in review of premarket applications and postmarketing regulation of particular products. We note that FDA currently interprets the standards in various medical and tobacco product premarket review pathways to refer to individual products rather than product categories, and the question of whether a particular product could obtain marketing authorization as both a tobacco product and as a medical product is beyond the scope of this rule. By clarifying the jurisdictional lines between tobacco and medical products, FDA believes that finalization of this rule will make it less likely that manufacturers will attempt to market products made or derived from tobacco both as tobacco products and as medical products--for example, if a tobacco product manufacturer attempts to add claims to a currently marketed tobacco product that would require the product to be regulated as drug, device, or combination product.

(Comment 33) Several comments recommended that the Center for Tobacco Products (CTP) have sole regulatory jurisdiction over tobacco and nicotine-containing products and provided suggestions for how CTP should structurally reorganize itself to better regulate these products.

(Response) CTP oversees the regulation of products made or derived from tobacco that are intended for human consumption. As stated in this preamble, when a product made or derived from tobacco is marketed or distributed for an intended use that falls within the drug/device definitions, it would be regulated as a medical product unless it is intended to affect the structure or any function of the body in any way related to the effects of nicotine that were commonly and legally claimed prior to March 21, 2000. In this situation, one of FDA's medical product centers would have regulatory oversight over these products because CTP does not

oversee the regulation of medical products. As these comments relate to potentially undertaking a structural re-organization, CTP is not considering a structural reorganization at this time.

(Comment 34) At least one comment suggested that FDA create a separate regulatory category for e-cigarettes that is based on the Agency's medical product regulations, but with less stringent quality standards.

(Response) This recommendation is not consistent with the statutory definitions in the FD&C Act. Under the FD&C Act, a product made or derived from tobacco is subject to regulation as a tobacco product unless it meets the definition of a drug or device or is a combination product, in which case it is subject to regulation as a medical product.

(Comment 35) Several comments stated that the cost and resources required to complete FDA's drug application process would be simply too great and would shut down many small manufacturers.

(Response) This regulation simply clarifies the circumstances under which a product made or derived from tobacco would be regulated as a drug, device, or combination product, and the circumstances under which it would be regulated as a tobacco product; it does not create new jurisdictional lines or impose new obligations on product manufacturers. Because the jurisdictional lines already exist, tobacco product manufacturers currently making claims that would render their product subject to regulation as a medical product or who wish to make such claims in the future are within FDA's drug and device jurisdiction, absent limited exceptions, and they must follow the applicable statutory and regulatory requirements.

(Comment 36) Many comments believed that the regulation would make e-cigarettes less available to consumers.

(Response) FDA disagrees. This regulation simply clarifies the circumstances under which a product made or derived from tobacco will be regulated as a drug, device, or combination product, and the circumstances under which it will be regulated as a tobacco product. This regulation will not add any additional burden to manufacturers who sell ENDS for recreational use. However, if a manufacturer is selling ENDS and making medical product claims, then the product would be subject to regulation as a drug, device, or combination product if those claims are not structure/function claims related to the effects of nicotine that were commonly and legally claimed prior to March 21, 2000.

(Comment 37) At least one comment suggested that the final rule should include a discussion of how the regulation will affect public health.

(Response) The preamble to the proposed rule contained some discussion of this topic, and this preamble to the final rule further expands on various public health protections.

(Comment 38) FDA proposed that a product made or derived from tobacco that is intended for use in smoking cessation be subject to regulation as a medical product. Several comments objected that smoking is not a disease, but a behavior, and that a product that claims to help individuals quit smoking should not be regulated as a medical product absent any assertions that it will prevent disease or treat nicotine dependence. One comment asserted that promoting a product as suitable for continued nicotine use after stopping smoking traditional cigarettes is the functional equivalent of a “smoking alternative” claim, which FDA has said does not fall within the Agency’s medical product authority, and, therefore, should not subject the product to regulation as a medical product.

(Response) Over the past 50 years, smoking has been causally linked to diseases of nearly all organs of the body, diminished health status, and fetal harm. Most current adult

smokers want to quit smoking completely for health reasons (Ref. 18). Given these facts, we believe that statements related to quitting smoking generally create a strong suggestion that a product is intended for a therapeutic purpose. We recognize, however, that public perception can change and evidence may be developed showing that, in some situations, “smoking cessation” is understood in context as referring to ending the use of traditional cigarettes and switching to a non-combustible product made or derived from tobacco. We have revised the codified language in § 1100.5(a) in the final rule, to reflect that “smoking cessation” is one type of intended use related to “the cure or treatment of nicotine addiction.” FDA intends to closely scrutinize “smoking cessation” claims to ensure that consumers are not misled about the intended use of a product made or derived from tobacco.

(Comment 39) One comment stated that this regulation should not require companies that handle raw materials to determine whether those raw materials would be used in tobacco products or whether those materials would be used in medical products. The comment stated that the intended use of the product is completely within the discretion of the sellers and distributors of the finished products, and the Agency should not extend regulations to cover companies that handle raw materials.

(Response) This comment is beyond the scope of this rule. This regulation does not create new jurisdictional lines or impose new obligations on product manufacturers or companies that handle raw materials. Rather, this rulemaking simply clarifies the circumstances under which a product made or derived from tobacco would be regulated as a drug, device, or combination product, and the circumstances under which it would be regulated as a tobacco product. If FDA were to consider extending its authority in such a way that would place

additional requirements on companies handling raw materials, the Agency would do so through a separate rulemaking.

#### F. Other Changes to the Codified Text

To eliminate redundancy, we deleted “or prevention or mitigation of disease” from the end of § 1100.5(a), as the opening text already includes similar language. Because of this deletion, we inserted the word “or” in front of “relief of nicotine withdrawal symptoms.”

#### G. Effective Date

This final rule will become effective 30 days after the date of its publication in the Federal Register. During those 30 days, manufacturers will continue to be under an obligation to comply with all applicable provisions of the FD&C Act and applicable regulations.

#### V. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the final rule does not contain policies that would 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, the Agency concludes that the final 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. Executive Order 13175: Tribal Consultation

We have analyzed this rule in accordance with the principles set forth in Executive Order 13175. We have determined that the rule does not contain policies that have substantial direct effects 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. Accordingly, we conclude that the rule does not contain policies that have tribal implications as defined in the Executive order and, consequently, a tribal summary impact statement is not required.

#### VII. Analysis of Environmental Impact

FDA has determined under 21 CFR 25.30(h) and (k) 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.

#### VIII. Economic Analysis of Impacts

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, 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). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because, as described in detail in the section entitled “Final Small Entity Analysis” in the full analysis of economic impacts available in the docket for this final rule (Ref. 19) and at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>, the clarifications in this final rule will not significantly increase costs on manufacturers of



products made or derived from tobacco, we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in expenditure in any year that meets or exceeds this amount.

The final rule will reduce ambiguity in the market for products made or derived from tobacco and clarify FDA’s interpretation and application of its existing intended use regulations. The rule clarifies the intended uses and supporting evidence that would result in these products being regulated as drugs, devices, or combination products rather than tobacco products. Products derived from tobacco that are intended to: (1) Diagnose, cure, mitigate, treat or prevent disease, including use in smoking cessation or (2) affect the structure or any function of the body in any way that is different from effects related to nicotine that were commonly and legally claimed in the marketing of cigarettes and smokeless tobacco prior to March 21, 2000, such as an intended use for improving respiratory function, will be subject to regulation as drugs, devices, or combination products. We estimate that there would be one-time costs for tobacco manufacturers to evaluate current product communications such as labeling and associated promotional materials in light of the clarifications in this final rule, and to revise them if needed.

We expect that only a small number of product communications such as labeling and associated materials will undergo a one-time change as a result of this rule.

The final rule will provide greater clarity to producers regarding the regulatory requirements for products made or derived from tobacco and to consumers to distinguish products intended for medical uses from those marketed for other uses. The reduction in ambiguity will enhance consumers' understanding of the products they purchase and may increase consumer welfare as a result.

Table 2.--Economic Data: Costs and Benefits Statement

Category	Primary Estimate	Low Estimate	High Estimate	Units			Notes
				Year Dollars	Discount Rate	Period Covered	
Benefits							
Annualized Monetized \$millions/year					7%		
					3%		
Annualized Quantified					7%		
					3%		
Qualitative	Reduce regulatory ambiguity						
Costs							
Annualized Monetized \$millions/year	\$0.246	\$1.126	\$0.365	2014	7%	10 years	
	\$0.202	\$0.202	\$0.202				
	\$0.202	\$0.104	\$0.301	2014	3%	10 years	
Annualized Quantified					7%		
					3%		
Qualitative							
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: No Effect							
Small Business: No effect							
Wages: No estimated effect							
Growth: No estimated effect							

The full analysis of economic impacts is available in the docket for this final rule (Ref. 19) and at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

#### IX. Paperwork Reduction Act of 1995

FDA concludes that this final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

#### X. References

The following references are on display in the Division of Dockets Management (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 Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. Defendants' Memorandum of Points and Authorities in Support of Motion to Dismiss or for Summary Judgment. Allergan Inc. v. United States of America, et al., 1:09-cv-01879-JDB (D.D.C. Jan. 11, 2010), 2010 WL 11211158.
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12. Kesselheim, A. S., and M.M. Mello, "Healthcare Decisions in the New Era of Healthcare Reform: Prospects for Regulation of Off-Label Drug Promotion in an Era of

Expanding Commercial Speech Protection,” North Carolina Law Review, 92:1539, 1585, 2014.

13. Stafford, R. S., “Regulating Off-Label Drug Use--Rethinking the Role of the FDA,” New England Journal of Medicine, 358:1427-1429, 2008.

14. President’s Cancer Panel, “Promoting Healthy Lifestyles,” 2007, available at <http://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp07rpt/pcp07rpt.pdf>.

15. Institute of Medicine of the National Academies, “Ending the Tobacco Problem: A Blueprint for the Nation,” 2007, available at <https://www.nap.edu/read/11795/chapter/1>.

16. Roditis, M. L., and B. Halpern-Felsher, “Adolescents’ Perceptions of Risks and Benefits of Conventional Cigarettes, E-Cigarettes and Marijuana: A Qualitative Analysis,” Journal of Adolescent Health, 57(2):179-185, 2015.

17. Vickerman, K. A., K. M. Carpenter, T. Altman, et al., “Use of Electronic Cigarettes Among State Tobacco Cessation Quitline Callers,” Nicotine & Tobacco Research, 15(10):1787-1791, 2013.

18. Gallup Consumption Habits poll, July 2013 (see <http://www.gallup.com/poll/163763/smokers-quit-tried-multiple-times.aspx>).

19. Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination; Amendments to Regulations Regarding “Intended Uses,” Final Rule; Final Regulatory Impact Analysis.

20. Janssen, W. F., “Outline of the History of U.S. Drug Regulation and Labeling,” Food Drug Cosmetic Law Journal, 36: 420, 437-438, 1981.

## List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 801

Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 1100

Combination products, Devices, Drugs, Smoking, Tobacco.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR chapter 1 is amended as follows:

## PART 201--LABELING

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

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 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 drugs. The intent is determined by such persons' expressions or may be shown 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. It may be shown, for example, by circumstances in which the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. 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 received the drug, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. And 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), he is required, in accordance with section 502(f) of the Federal Food, Drug, and Cosmetic Act, or, as applicable, duly promulgated regulations exempting the drug from the requirements of section 502(f)(1), to provide for such drug adequate labeling that accords with such other 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 devices. The intent is determined by such persons' expressions or may be shown 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. It may be shown, for example, by circumstances in which the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. 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 received the device, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. And if the totality of the evidence establishes that a manufacturer objectively intends that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than ones for which it has been approved, cleared, granted marketing authorization, or is exempt from premarket notification requirements (if any), he is required, in accordance with section 502(f) of the Federal Food, Drug, and Cosmetic Act, or, as applicable, duly promulgated regulations exempting the device from the requirements of section 502(f)(1), to provide for such device adequate labeling that accords with such other intended uses.

#### PART 1100--TOBACCO PRODUCTS SUBJECT TO FDA AUTHORITY

5. The authority citation for part 1100 is revised to read as follows:

Authority: 21 U.S.C. 387a(b), 387f(d); Secs. 901(b) and 906(d), Pub. L. 111-31; 21 CFR 16.1 and 1107.1; 21 CFR 1.1, 1.20, 14.55, 17.1, and 17.2. Section 1100.5 is issued under 21 U.S.C. 321, 353(g), and 371(a); 21 CFR 1.1.

6. Part 1100 is amended by adding § 1100.5 to read as follows:

§ 1100.5 Exclusion from tobacco regulation.

If a product made or derived from tobacco that is intended for human consumption is intended for use for any of the purposes described in paragraph (a) or (b) of this section, the product is not a tobacco product as defined in section 201(rr) of the Federal Food, Drug, and Cosmetic Act and will be subject to regulation as a drug, device, or combination product.



(a) The product is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, including use in the cure or treatment of nicotine addiction (e.g., smoking cessation), relapse prevention, or relief of nicotine withdrawal symptoms;

(b) The product is intended to affect the structure or any function of the body in any way that is different from effects related to nicotine that were commonly and legally claimed in the marketing of cigarettes and smokeless tobacco products prior to March 21, 2000.

Dated: December 29, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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