

Body system listings	Current expiration date	Extended expiration date
Neurological Disorders (11.00 and 111.00) .....	September 29, 2021 .....	September 29, 2025.

We continue to revise and update the listings on a regular basis, including those body systems not affected by this final rule.<sup>2</sup> We intend to update the listings affected by this final rule as necessary based on medical advances as quickly as possible, but may not be able to publish final rules revising these listings by the current expiration date. Therefore, we are extending the expiration date listed above.

## Regulatory Procedures

### Justification for Final Rule

We follow the Administrative Procedure Act (APA) rulemaking procedures specified in 5 U.S.C. 553 in promulgating regulations. Section 702(a)(5) of the Social Security Act, 42 U.S.C. 902(a)(5). Generally, the APA requires that an agency provides prior notice and opportunity for public comment before issuing a final regulation. The APA provides exceptions to the notice-and-comment requirements when an agency finds there is good cause for dispensing with such procedures because they are impracticable, unnecessary, or contrary to the public interest.

We determined that good cause exists for dispensing with the notice and public comment procedures. 5 U.S.C. 553(b)(B). This final rule only extends the date on which the Neurological Disorders body system listings will no longer be effective. It makes no substantive changes to our rules. Our current regulations<sup>3</sup> provide that we may extend, revise, or promulgate the body system listings again. Therefore, we determined that opportunity for prior comment is unnecessary, and we are issuing this regulation as a final rule.

In addition, for the reasons cited above, we find good cause for dispensing with the 30-day delay in the effective date of this final rule. 5 U.S.C. 553(d)(3). We are not making any substantive changes to the Neurological Disorders body system listing. Without an extension of the expiration date for this listing, we will not have the criteria we need to assess medical impairments in the body system at step three of the sequential evaluation processes. We

therefore find it is unnecessary to delay the effective date of this final rule.

### Executive Order 12866, as Supplemented by Executive Order 13563

We consulted with the Office of Management and Budget (OMB) and determined that this final rule does not meet the requirements for a significant regulatory action under Executive Order 12866, as supplemented by Executive Order 13563. Therefore, OMB did not review it. We also determined that this final rule meets the plain language requirement of Executive Order 12866.

### Regulatory Flexibility Act

We certify that this final rule does not have a significant economic impact on a substantial number of small entities because it affects only individuals. Therefore, a regulatory flexibility analysis is not required under the Regulatory Flexibility Act, as amended.

### Paperwork Reduction Act

These rules do not create any new or affect any existing collections and, therefore, do not require Office of Management and Budget approval under the Paperwork Reduction Act.

(Catalog of Federal Domestic Assistance Program Nos. 96.001, Social Security—Disability Insurance; 96.002, Social Security—Retirement Insurance; 96.004, Social Security—Survivors Insurance; 96.006, Supplemental Security Income)

### List of Subjects in 20 CFR Part 404

Administrative practice and procedure, Blind, Disability benefits, Old-Age, Survivors and Disability Insurance, Reporting and recordkeeping requirements, Social Security.

The Acting Commissioner of the Social Security Administration, Kilolo Kijakazi, having reviewed and approved this document, is delegating the authority to electronically sign this document to Faye I. Lipsky, who is the primary Federal Register Liaison for SSA, for purposes of publication in the **Federal Register**.

**Faye I. Lipsky,**

*Federal Register Liaison, Office of Legislative and Congressional Affairs, Social Security Administration.*

For the reasons set out in the preamble, we are amending subpart P of part 404 of chapter III of title 20 of the Code of Federal Regulations as set forth below.

## PART 404—FEDERAL OLD-AGE, SURVIVORS AND DISABILITY INSURANCE (1950— )

### Subpart P—[Amended]

■ 1. The authority citation for subpart P of part 404 continues to read as follows:

**Authority:** Secs. 202, 205(a)–(b) and (d)–(h), 216(i), 221(a) and (h)–(j), 222(c), 223, 225, and 702(a)(5) of the Social Security Act (42 U.S.C. 402, 405(a)–(b) and (d)–(h), 416(i), 421(a) and (h)–(j), 422(c), 423, 425, and 902(a)(5)); sec. 211(b), Pub. L. 104–193, 110 Stat. 2105, 2189; sec. 202, Pub. L. 108–203, 118 Stat. 509 (42 U.S.C. 902 note).

■ 2. Amend appendix 1 to subpart P of part 404 by revising item 12 of the introductory text before Part A to read as follows:

### Appendix 1 to Subpart P of Part 404—Listing of Impairments

\* \* \* \* \*

12. Neurological Disorders (11.00 and 111.00): September 29, 2025.

\* \* \* \* \*

[FR Doc. 2021–16417 Filed 7–30–21; 8:45 am]

**BILLING CODE 4191–02–P**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

#### 21 CFR Parts 201 and 801

[Docket No. FDA–2015–N–2002]

RIN 0910–AI47

### Regulations Regarding “Intended Uses”

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA, the Agency, or we) is issuing a final rule to amend its medical product “intended use” regulations. This final rule amends FDA’s regulations describing the types of evidence relevant to determining whether a product is intended for use as a drug or device under the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Public Health Service Act (PHS Act), and FDA’s implementing regulations, including whether a medical product that is approved, cleared, granted marketing authorization, or exempted from

<sup>2</sup> We last revised the expiration date for the Neurological Disorders body system listings when we updated the body system on July 1, 2016 (81 FR 43038, 43052).

<sup>3</sup> See the first sentence of appendix 1 to subpart P of part 404 of 20 CFR.

premarket notification is intended for a new use. This action also withdraws and replaces the portions of a final rule issued on January 9, 2017, that never became effective.

**DATES:** This rule is effective September 1, 2021.

**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 Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

**FOR FURTHER INFORMATION CONTACT:** Kelley Nduom, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-5400, [kelly.nduom@fda.hhs.gov](mailto:kelly.nduom@fda.hhs.gov).

**SUPPLEMENTARY INFORMATION:**

**Table of Contents**

- I. Executive Summary
  - A. Purpose of the Final Rule
  - B. Summary of the Major Provisions of the Final Rule
  - C. Legal Authority
  - D. Costs and Benefits
- II. Meaning of Certain Terms in This Preamble
- III. Background
  - A. Introduction and History of This Rulemaking
  - B. Summary of Comments to the Proposed Rule
- IV. Legal Authority
- V. Comments on the Proposed Rule and FDA Responses
  - A. Introduction
  - B. Comments and Responses Regarding Statutory and Regulatory Authority
  - C. Comments and Responses Regarding the Design or Composition of an Article
  - D. Comments and Responses Regarding the First Amendment
  - E. Comments and Responses Regarding the Fifth Amendment
  - F. Comments and Responses Regarding Definitions
  - G. Comments and Responses Regarding "Safe Harbors"
  - H. Comments and Responses Regarding Examples
  - I. Comments on Codified Text and FDA Responses
  - J. Comments Recommending That FDA Expand the Scope of This Rulemaking

- VI. Effective Date
- VII. Economic Analysis of Impacts
  - A. Introduction and Summary
  - B. Final Economic Analysis of Impacts
  - C. Final Small Entity Analysis
- VIII. Analysis of Environmental Impact
- IX. Paperwork Reduction Act of 1995
- X. Federalism
- XI. Consultation and Coordination With Indian Tribal Governments
- XII. References

**I. Executive Summary**

*A. Purpose of the Final Rule*

FDA is taking this action to amend its existing regulations (§§ 201.128 and 801.4 (21 CFR 201.128 and 801.4)) describing the types of evidence relevant to determining a product's intended uses under the FD&C Act, the PHS Act, and FDA's implementing regulations. The amended regulations better reflect the Agency's current practices in evaluating whether a product is intended for use as a drug or device, including whether a medical product that is approved, cleared, granted marketing authorization, or exempted from premarket notification is intended for a new use. This action withdraws the portions of the final rule issued on January 9, 2017 (82 FR 2193), that never became effective, and it finalizes amendments to the intended use regulations for medical products that provide more clarity and direction to regulated industry and other stakeholders regarding the types of evidence relevant to determining a product's intended uses.

*B. Summary of the Major Provisions of the Final Rule*

FDA is finalizing amendments to its intended use regulations for medical products (§§ 201.128 and 801.4) to better reflect the Agency's current practices in evaluating whether a product is intended for use as a drug or device, including whether a medical product that is approved, cleared, granted marketing authorization, or exempted from premarket notification is intended for a new use.

Several comments on the proposed rule raised legal concerns. Some commenters argued that FDA should construe its statutory and regulatory authorities more narrowly, and some asserted that the proposed rule violates

the First and Fifth Amendments. These and similar arguments have been raised in comments received during earlier stages of this rulemaking as well as in other rulemaking proceedings, petitions, and litigation involving intended use issues. A number of other comments raised questions about the rule's applicability to certain medical devices, such as devices that are exempt from premarket notification (510(k)) requirements. These comments also criticized the inclusion of language in the regulation clarifying that the design or composition of an article may be relevant to determining its intended use.

The final rule remains largely unchanged from the proposed rule. In response to comments received, we have modified the codified language of the intended use regulation for medical devices to clarify its applicability to devices that are approved, cleared, granted marketing authorization, or exempted from premarket notification. That is the only change from the codified language in the proposed rule.

*C. Legal Authority*

Among the provisions that provide authority for this final rule are sections 201, 403(r), 503(g), and 701(a) of the FD&C Act (21 U.S.C. 321, 343(r), 353(g), 371(a)); section 5(b)(3) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)); and sections 215, 301, 351(i) and (j), and 361 of the PHS Act (42 U.S.C. 216, 241, 262(i) and (j), and 264).

*D. Costs and Benefits*

The benefit of this final rule is the added clarity and certainty for firms and stakeholders regarding the evidence relevant to establishing whether a product is intended for use as a drug or device, including whether a medical product that is approved, cleared, granted marketing authorization, or exempted from premarket notification is intended for a new use. We do not have evidence that the final rule will impose costs on currently marketed products.

**II. Meaning of Certain Terms in This Preamble**

As used in this rulemaking, the following terms have the meanings noted below.

Term	Meaning
A medical product that is approved, cleared, granted marketing authorization, or exempted from premarket notification.	This term refers to a medical product that may be legally introduced into interstate commerce for at least one use under the FD&C Act or the PHS Act as a result of having satisfied applicable premarket statutory and regulatory requirements.

Term	Meaning
A medical use that is approved, cleared, granted marketing authorization, or exempted from premarket notification.	This term refers to an intended use included in the required labeling for an FDA-approved medical product, an intended use included in the indications for use statement for a device cleared or granted marketing authorization by FDA, or an intended use of a device that falls within an exemption from premarket notification.
Firms .....	This term refers to manufacturers, packers, and distributors of FDA-regulated products and all their representatives, including both individuals and corporate entities.
Healthcare providers .....	This term refers to individuals such as physicians, veterinarians, dentists, physician assistants, nurse practitioners, pharmacists, or registered nurses who are licensed or otherwise authorized by the State to prescribe, order, administer, or use medical products in a professional capacity.
Medical products .....	This term refers to drugs and devices, including human biological products.
Products unapproved for any medical use .....	This term refers to medical products that are not approved, cleared, granted marketing authorization, or exempted from premarket notification (as that phrase is described above) by FDA for any medical use, and which must be approved, cleared, granted marketing authorization, or exempted from premarket notification to be legally marketed for such use. This term also includes products that are marketed for non-medical uses, such as dietary supplements, conventional foods, and cosmetics.
Unapproved use of a medical product that is approved, cleared, granted marketing authorization, or exempted from premarket notification.	This term refers to an intended use that is not included in the required labeling of an FDA-approved medical product, an intended use that is not included in the indications for use statement for a device cleared or granted marketing authorization by FDA, or an intended use of a device that does not fall within an exemption from premarket notification.

### III. Background

#### A. Introduction and History of This Rulemaking

The Agency issued a proposed rule in 2015 and a final rule in 2017 revising the language of its medical product intended use regulations, with the intent to conform them to the Agency's current practice in applying the regulations (see final rule, "Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding 'Intended Uses'" (82 FR 2193, January 9, 2017)). These amendments did not reflect a change in FDA's approach regarding types of evidence of intended use for drugs and devices. However, after receiving a petition that requested the Agency reconsider these amendments, FDA delayed the effective date of the 2017 final rule and reopened the docket to invite public comment. A number of comments submitted during the reopening raised questions and, on March 16, 2018 (83 FR 11639), FDA delayed the effective date of the intended use amendments until further notice to allow further consideration of the substantive issues raised in the comments received. After considering the issues raised in the petition and comments submitted during the reopening, FDA issued a notice of proposed rulemaking in September 2020

(85 FR 59718, September 23, 2020, the "NPRM") to withdraw the portions of the final rule issued on January 9, 2017, that never became effective and to propose a new rule to provide more clarity regarding the types of evidence that are relevant in determining a product's intended uses.

#### B. Summary of Comments to the Proposed Rule

Approximately 15 comments on the proposed rule were submitted to the docket. These comments were submitted by various industry trade organizations, consumer advocacy groups, and individuals. Several comments raised legal concerns with the proposed rule, including arguments to the effect that the rule violates the First and Fifth Amendments. Other comments raised questions and concerns about the rule's applicability to certain medical devices, such as devices that are 510(k)-exempt. These comments also generally objected to the inclusion of language in the regulation clarifying that the design or composition of an article may be relevant to determining its intended use.

### IV. Legal Authority

Among the statutory provisions that provide authority for this final rule are sections 201, 403(r), 503(g), and 701(a) of the FD&C Act, section 5(b)(3) of the Orphan Drug Act, and section 351(i) of

the PHS Act. Section 201 of the FD&C Act defines "drug" (subsection (g)(1)), "device" (subsection (h)), "food" (subsection (f)), "dietary supplement" (subsection (ff)), "cosmetic" (subsection (i)), and "tobacco product" (subsection (rr)(1)); section 5(b)(3) of the Orphan Drug Act defines "medical food"; and section 503(g)(1) of the FD&C Act provides that combination products are those "that constitute a combination of a drug, device, or biological product." Section 351(i) of the PHS Act defines "biological products", and section 351(j) of the PHS Act provides that the requirements of the FD&C Act apply to biological products. Section 403(r) of the FD&C Act establishes the requirements under which certain labeling claims about uses of conventional foods and dietary supplements to reduce the risk of a disease or affect the structure or function of the human body are not evidence of intended use as a drug. 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 regulates the manufacture, sale, and distribution of drugs, devices, combination products, tobacco products, foods (including dietary supplements), and cosmetics under the authority of the FD&C Act.

## V. Comments on the Proposed Rule and FDA Responses

### A. Introduction

We received approximately 15 comment submissions on the proposed rule by the close of the comment period, each containing one or more comments on one or more issues. We describe and respond to the comments in sections B through J of this section. We have numbered each comment to help distinguish between different comments. We have grouped similar comments together under the same number, and, in some cases, we have separated different issues discussed in the same comment and designated them as distinct comments for purposes of our responses. The number assigned to each comment or comment topic is purely for organizational purposes and does not signify the comment's value or importance or the order in which comments were received.

In addition to the comments specific to this rulemaking that we address in the following paragraphs, we received several general comments expressing support for 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. To the extent that comments expressing opposition to the rule requested that we refrain from finalizing the rule, we decline to do so. In general, comments outside the scope of this rulemaking have not been addressed here. Summaries of the remaining comments, as well as FDA's responses, are included in this document.

### B. Comments and Responses Regarding Statutory and Regulatory Authority

(Comment 1) One comment asserted that under the relevant statutes, legislative history, and case law, evidence of intended use is limited to promotional claims that have been made in the marketplace. The comment argued that the NPRM was wrong in stating that evidence of intended use can be derived from "any relevant source," including "circumstances surrounding distribution." Other comments also encouraged the Agency to focus primarily or only on promotional claims.

(Response) We disagree. Nothing in the statute requires the narrow scope that the comment suggested. Although the first comment mentioned above loosely refers to the statutory and regulatory regime as support for its preferred interpretation, it does not cite any statutory language that dictates an

exclusively claims-based approach to intended use. As four justices of the Supreme Court recognized in rejecting the argument that the statute limits evidence of intended use to promotional claims: "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 fact that intended use can be established through promotional claims does not preclude the possibility that other evidence may be relevant as well.

Nor does the comment cite any legislative history that supports an exclusively claims-based approach to intended use. Indeed, the legislative history supports reliance on evidence of use by healthcare practitioners and consumers as relevant to intended use. The House Report on the Medical Device Amendments of 1976 states that "[t]he Secretary may consider . . . use of a product in determining whether or not it is a device" (see H.R. Rep. 853, 94th Cong., 2d Sess. 14 (1976), reprinted in *An Analytical Legislative History of the Medical Device Amendments of 1976*, Appendix III (Daniel F. O'Keefe, Jr. and Robert A. Spiegel, eds. 1976)). Similarly, the legislative history of the 1938 Act states expressly that "the use to which the product is to be put will determine the category into which it will fall" (see S. Rep. No. 361, 74th Cong., 1st Sess. 4 (1935), reprinted in 3 *Legislative History* 660, 663).

Nor does the language of the existing regulation support the commenter's position. "[N]owhere does the regulation state that" evidence of intended use is limited to statements or claims "published to the marketplace" (see *United States v. Vascular Solutions, Inc.*, 181 F. Supp. 3d 342, 347 (W.D. Tex. 2016)). Indeed, the existing regulations specifically state that evidence of intended use includes "circumstances surrounding the distribution of the article" and "circumstances that the article . . . is offered or used for a purpose for which it is neither labeled or advertised." This language was included when the regulation was first codified in 1952 (see 17 FR 6818, 6820 (1952) (Ref. 1)).

Furthermore, the case law does not resolve the matter in favor of the position advanced by the commenter. Courts have repeatedly held that intended use is determined by looking to any 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, such as the identit[y] of actual customers and their use of the product and labeling claims, 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) (internal citations omitted)).

Courts have rejected the commenter's 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, . . . '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 at 347 (the position that evidence of objective intent is limited to statements “published to the marketplace” is “absurd[ ]”); 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 product[ ]’s labelling states that it is not a drug”); *United States v. 22 Rectangular or Cylindrical Finished Devices*, 714 F. Supp. 1159, 1165 (D. Utah 1989) (“The objective intent referred to in the regulation may be shown not only by a product’s labeling claims, advertising or written statements relating to the circumstances of a product’s distribution, . . . but also by a product’s actual use. See H.R. Rep. No. 853, 94th Cong., 14 (1976). . . . There also can be no dispute that the sterilizer, in its actual use, plays an integral role in the surgical treatment of patients.”); *Hanson v. United States*, 417 F. Supp. 30, 35 (D. Minn. 1976) (finding plaintiffs’ beliefs that many people will die if they are deprived of the tablets and vials at issue relevant to establishing intended use), *aff’d*, 540 F.2d 947 (8th Cir. 1976); *United States v. Device Labeled “Cameron Spittler Amblyo-Syntonizer”*, 261 F. Supp. 243, 245 (D. Neb. 1966) (“While claimant contends that the machines have not been represented as a cure for any particular eye malfunction, he admits the use of them in the treatment of certain eye maladies. Clearly, the seized machines are each a device within the meaning of § 321(h).”).

Although one comment cited to several cases that relied only on promotional claims as evidence of intended use, only a very few, if any, cases have actually excluded non-claims evidence from consideration as evidence of intended use on the ground that the evidence was not promotional. The presence of claims may be particularly significant in determining intended use where a product, such as honey, does not have a therapeutic benefit or physiological effect (see, e.g., *United States v. An Article . . . “U.S. Fancy Pure Honey”*, 218 F. Supp. 208, 211 (E.D. Mich. 1963) (claim that honey is a panacea for various diseases and ailments established the intended use as a drug), *aff’d*, 344 F.2d 288 (6th Cir. 1965). But the converse is *not* true—the absence of claims on a product that does have a physiological effect will not automatically render the product immune from FDA jurisdiction (see, e.g., *United States v. Carlson*, 810 F.3d 544 (8th Cir. 2016) (synthetic drugs, such as synthetic marijuana, labeled as incense, herbal incense, herbal potpourri, bath salts, etc., and that also bore the statement “not for human consumption,” found to be subject to FDA’s jurisdiction as drugs)).

As FDA has explained, limiting evidence of intended use to only promotional claims would allow manufacturers to circumvent FDA regulation by masking their true intent, either by simply omitting explicit promotional claims or by making claims that are not true (for example, “not for human use”). See 82 FR 14319 at 14321 through 14322 (March 20, 2017); 82 FR 2193 at 2196 (January 9, 2017); 80 FR 57756 at 57757 (September 25, 2015). 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)). This is an issue that comes up frequently with respect to products in domestic commerce as well as imported goods and has resulted in FDA-issued warning letters, import refusals, civil injunction actions, and criminal prosecutions. FDA believes it is worth repeating the following previously cited examples, see 82 FR 14319 at 14321 through 14322 (March 20, 2017), of the types of situations in which evidence of intended use has been derived from sources other than explicit promotional claims:

- Persons distributing substances that are known to be used recreationally to achieve a mind-altering effect, such as dextromethorphan (the active ingredient

in some cough suppressants) and nitrous oxide (which is a prescription drug) (see, e.g., *United States v. Johnson*, 471 F.3d 764, 765 (7th Cir. 2006); *United States v. Schraud*, 2007 U.S. Dist. LEXIS 89231, 3–6 (E.D. Mo. December 4, 2007); *United States v. Travia*, 180 F. Supp. 2d 115, 119 (D.D.C. 2001); *United States v. LA Rush*, 2:13-cr-00249, First Superseding Information (C.D. Cal. April 3, 2014)).

- Persons distributing synthetic drugs, such as synthetic marijuana, labeled as incense, potpourri, bath salts, and/or bearing the statement “not for human consumption” (see, e.g., *United States v. Carlson*, 810 F.3d 544 (8th Cir. 2016); *United States v. Carlson*, 12-cr-00305–DSD–LIB, Amended Superseding Indictment (D. Minn. Sept. 11, 2013) and Court’s Instructions to the Jury, (D. Minn. October 8, 2013); *United States v. Bowen*, 14-cr00169–PAB, Indictment (D. Colo. May 5, 2014) and Rule 11(c)(1)(A) and (B) Plea Agreement and Statement of Facts Relevant to Sentencing (D. Colo. January 29, 2015).

- Persons distributing imitation drugs claimed to be incense or dietary supplements, such as imitation cocaine or imitation Ecstasy (see, e.g., *United States v. Storage Spaces Designated Nos. “8” & “49”*, 777 F.2d 1363, 1366 (9th Cir. 1985); *United States v. Undetermined Quantities of . . . Street Drug Alternatives*, 145 F. Supp. 2d 692 (D. Md. 2001)).

- Persons distributing products containing the active ingredients in prescription drugs, such as VIAGRA, CIALIS, LEVITRA, or BOTOX, as less expensive alternatives to the approved products, with labeling that states that they are “all natural” or “herbal” supplements or “for research only” (see, e.g., *United States v. Dessart*, 823 F.3d 395 (7th Cir. 2016); *United States v. Zeyid*, 1:14-cr-0197, First Superseding Indictment (N.D. Ga. June 24, 2014) (see also Ref. 2); *United States v. Livdahl*, 459 F. Supp. 2d 1255, 1260 (S.D. Fla. 2005)).

Other instances where a person’s claims about the intended use of a product are belied by the person’s activities or non-promotional statements or by circumstantial evidence (see, e.g., *United States v. An Article of Device Toftness Radiation Detector*, 731 F.2d 1253, 1257 (7th Cir. 1984); *United States v. 789 Cases of Latex Surgeons’ Gloves*, 799 F. Supp. 1275, 1294–1295 (D.P.R. 1992)).

In these situations, the evidence relied on to establish intended use has included general knowledge of actual use by customers to achieve a mind-altering effect; the known effects of a product or substance; implied claims

from using names that sound similar to the names of controlled substances; the circumstances surrounding the sale (e.g., a rock concert venue; receiving the product in bulk and repackaging into smaller plastic bags; the use of private email addresses; the absence of labeling); shipping orders, other correspondence, and memoranda relating to marketing and distribution; statements made in training sessions; and admissions.

Evidence other than promotional claims has also been used to establish that products offered for import into the United States without labeling or other claims that identify them as a drug or device are in fact intended for use as a drug or device and are therefore subject to refusal if it appears that they fail to meet certain requirements for importing medical products (see 21 U.S.C. 381(a)(3)). For example, the defendants in *United States v. Zeyid*, 1:14-cr-0197, First Superseding Indictment (N.D. Ga. June 24, 2014) (see Ref. 2), imported products containing active ingredients that were the same as those used in prescription drugs but that were labeled as “tea,” “coffee,” and “beauty products.”

(Comment 2) One comment asserted that the position on intended use described by FDA in the NPRM was an “alternative, novel interpretation [] with which FDA has flirted from time to time in the past.”

(Response) We disagree. This is not the first time FDA has responded to arguments that its interpretation of the scope of evidence relevant to “intended use” is too broad—those arguments have been raised in comments in earlier stages of this and other rulemaking proceedings, petitions, and litigation involving intended use issues. Contrary to the comment’s assertion that the NPRM presented a novel interpretation of intended use, FDA has steadfastly maintained for decades that, in determining a product’s intended use, the Agency may look to any relevant source of evidence, including a variety of direct and circumstantial evidence. FDA’s position is reflected in the notices issued in this rulemaking over the past 5 years (see, e.g., 85 FR 59718 at 59721 (September 23, 2020); 82 FR 14319 at 14320 (March 20, 2017); 82 FR 2193 at 2206 (January 9, 2017); 80 FR 57756 at 57757 (September 25, 2015)), and has been noted in court decisions (see, e.g., *Spectrum Pharma. v. Burwell*, 824 F.3d 1062, 1069 (D.C. Cir. 2016) (“To be sure, FDA recognizes that there may be situations in which it will look beyond just the manufacturer’s statements [to determine intended use].”); *United States v. Travia*, 180 F.

Supp. 2d 115, 119 (D.D.C. 2001) (“The government argues that the Court should look to the objective intent of the sellers in this case, which would permit the Court to view the totality of the circumstances—namely, the selling of balloons of laughing gas in the parking lot at a rock concert—surrounding the sale of the nitrous oxide here. See, e.g., 21 CFR 201.128.”)). This position has also been explained in numerous litigation briefs and other FDA pronouncements, such as in the following excerpts from examples of such documents issued from 2000 to 2017:

- In determining a product’s intended uses, “[l]abeling is not [the] exclusive evidence.” See *United States v. Travia*, 180 F. Supp. 2d 115, 119 (D.D.C. 2001). Instead, “it is well established that the ‘intended use’ of a product, within the meaning of the Act, is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source.” *Action on Smoking and Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980) (quotation marks omitted); see also *V.E. Irons, Inc. v. United States*, 244 F.2d 34, 44 (1st Cir. 1957) (“[W]e are free to look to all relevant sources in order [to] ascertain what is the ‘intended use’ of a drug.”). Courts have considered “relevant sources” to include, for example, product formulation and method of intake, actual use of the product by consumers and medical practitioners, and circumstances of sale in determining intended use. See, e.g., *United States v. Ten Cartons, More or Less, of an Article . . . Ener-B Vitamin B-12*, 72 F.3d 285, 287 (2d Cir. 1995); *United States v. Storage Spaces*, 777 F.2d 1363, 1367 (9th Cir. 1985); *United States v. An Article of Device . . . Toftness Radiation Detector*, 731 F.2d 1253, 1257–58 (7th Cir. 1984) (Litigation brief (2011), Ref. 3).

- Courts have recognized that intended use may be shown by non-speech evidence that has included, for example, product formulation and method of intake, actual use of the product by consumers and medical practitioners, and circumstances of sale (Litigation brief (2010), Ref. 4 at 8–9 n.5).

- Courts have repeatedly held that, although promotional claims are one source of evidence of intended use, FDA is authorized to rely on any other relevant source of evidence [including] . . . [the product’s] method of intake, . . . [how any claims are] understood by a consumer. . . . [suggestive] product names, . . . [and] meta-tags (Litigation brief (2001), Ref. 5 at 20–26).

- [Evidence of intended use to be presented at trial includes:] (1) Defendant intended the nitrous oxide he was offering for sale on his website bongmart.com to be used as a drug, despite his marking the nitrous oxide ‘For Food Use Only;’ (2) Defendant knew that the nitrous oxide cartridges were commonly used as a drug for getting high; and (3) Defendant’s customers actually used the nitrous oxide sold by Defendant as a drug (Litigation brief (2000), Ref. 6 at 6).
- It has been the Agency’s longstanding position that in determining a product’s intended use, the Agency may look to any relevant source of evidence. . . . To hold accountable firms that attempt to evade FDA drug jurisdiction by avoiding making express claims about their products or disclaiming a particular intended use, courts have relied on a variety of evidence to establish intended use, including general knowledge of actual use by customers to get high or have some other mind-altering effect; the known effects of a product or substance; implied claims from using names that sound similar to controlled substances; the circumstances surrounding the sale (e.g., a rock concert venue; receiving the product in bulk and repackaging into smaller plastic bags; the use of private email addresses; the absence of labeling); shipping orders, other correspondence, and memoranda relating to marketing and distribution; statements made in training sessions; and admissions (Regulatory letter (2017), Ref. 7 at 9–10).

- The manufacturer’s intent will necessarily be determined on a case-by-case basis, looking at the totality of the facts and circumstances. . . . The trier of fact will take into account the full body of evidence. If evidence of distribution or sponsorship activity forms part of the basis of FDA’s claim, the trier of fact will consider the context of that activity . . . in assessing the manufacturer’s objective intent (Regulatory letter (2002), Ref. 8 at 6).<sup>1</sup>

In addition, issues involving the scope of evidence relevant to establishing intended use frequently arise in FDA’s day-to-day operations in protecting the public health, including Warning Letters and import determinations (see, e.g., FDA Warning

<sup>1</sup> The comment erroneously asserts that FDA’s reliance on evidence other than promotional claims to assert jurisdiction over cigarettes in a 1996 final rule was “roundly rejected by the courts.” In fact, the Supreme Court’s majority opinion declined to address the issue, and the dissent endorsed FDA’s analysis (see *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 131–32 (2000); *id.* at 170 (dissenting opinion)).

Letter to HelloCig Electronic Technology Co., Ltd (Ref. 9) (relying in part on undeclared active pharmaceutical ingredient as well as implied claims from imagery to determine product's intended use); FDA Warning Letter to Duy Drugs, Inc. (Ref. 10) (relying in part on undeclared sildenafil to establish intended use); Letter from Steven B. Barber, District Director, Cincinnati District, FDA to Marc C. Sanchez, Esq., Mood and Mind, LLC, (Ref. 7 at 9–10) (relying in part on known attributes and common uses of product to establish use); Letter from Daniel Solis, Director, Import Operations Branch, Los Angeles District to Carol A. Pratt, K&L Gates LLP (Ref. 11) (relying in part on information available on the internet reflecting general understanding by consumers of mind-altering properties and purported medical uses of product, as well as pattern of changes to the importer's website and blog to conceal the true intended use of the product by deleting references to the amount of a psychoactive component in the product); FDA Warning Letter to Lifetech Resources Labs Inc. (Ref. 12) (relying in part on “presence of the prostaglandin analog, isopropyl cloprostenate, along with appearance claims” to establish intended use); FDA Warning Letter to INZ Distributors (Ref. 13) (relying in part on presence of analogue of an erectile dysfunction drug to determine product's intended use)). One of the purposes of this rulemaking is to put to rest any dispute about FDA's interpretation of its statute and regulations, and its policy—as embodied in this rule as well as in the precedent cited above—regarding evidence that may be relevant to establishing intended use.

(Comment 3) With respect to the many situations where manufacturers and distributors attempt to evade FDA regulatory oversight by omitting promotional medical product claims, examples of which are provided above, one comment suggested that the Government could use other regulatory tools rather than apply FDA's authorities for premarket review of medical products. Specifically, the comment suggested that FDA employ “a combination of post-market risk mitigation techniques” which would require FDA to engage in the “collection, review, and potential description in labeling” of the risks associated with the “unlabeled use” before taking enforcement action against the product to protect the public health. The same comment suggested that, alternatively, FDA could consider

evidence other than promotional claims, but only to establish that in fact a promotional claim had been made.

(Response) FDA declines this suggestion. The fundamental purpose of the FD&C Act is to help protect “the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection” (*United States v. Dotterweich*, 320 U.S. 277, 280 (1943)). “[R]emedial legislation such as the Food, Drug, and Cosmetic Act is to be given a liberal construction consistent with the Act's overriding purpose to protect the public health” (*United States v. An Article of Drug . . . Bacto Unidisk*, 394 U.S. 784, 798 (1969)). Although FDA generally considers risk as part of its determination whether to take enforcement action, part of the impetus for Congress' development of the premarket review requirements was the determination that exclusive reliance on postmarket remedies, such as enforcement actions for false or misleading labeling, is inadequate because it does not prevent consumers from experiencing harm from unsafe and/or ineffective treatments.

FDA's position regarding evidence relevant to establishing intended use helps protect the public health. To describe more fully one of the examples cited above: In *United States v. Johnson*, 471 F.3d 764 (7th Cir. 2006), the defendant imported dextromethorphan hydrobromide (DXM), the active ingredient in some cough suppressants, and distributed it for recreational use. During the 4 months his company was in operation, five customers died. Because DXM is not a controlled substance, no charges were brought under the Controlled Substances Act, but the court found that FDA had jurisdiction under the FD&C Act (id. at 765). Defendant pleaded guilty to three counts of introducing a misbranded drug into interstate commerce and received a 77-month sentence (id.). In upholding that sentence, the Seventh Circuit noted that the defendant “knew—not merely should have known—that there was a substantial risk that more of his customers would die, and yet he continued to sell DXM for recreational use and failed to warn existing customers, including the two teenagers who died after he learned of the first two deaths” (id.).

Because FDA's position on intended use helps ensure that it can help curb the distribution of dangerous and fraudulent products, FDA declines to construe intended use more narrowly than the statute provides.

(Comment 4) One comment objected to FDA's statement in the proposed rule

that relying exclusively on firms' claims to determine intended use would adversely affect public health by opening the door to the marketing of products that are unapproved for any medical use. The comment argued that there is no public health need for FDA to rely on evidence other than express claims to determine intended use because the FD&C Act and other statutes provide other authorities that allow FDA to take action against products that contain an active ingredient from an FDA-approved drug, controlled substance, or other pharmacological ingredient. Specifically, the comment recommended that FDA use its dietary supplement and food additive authorities to keep products containing pharmacological ingredients out of dietary supplements and conventional foods, rather than using an intended use analysis to classify and regulate the products as drugs. The specific authorities mentioned in the comment were the definitions of “food” and “dietary supplement” and the corresponding adulteration provisions of the FD&C Act; the premarket notification requirement for certain dietary ingredients not marketed in the United States before October 15, 1994; and the premarket approval requirement for food additives. Similarly, another comment argued that rather than continuing to take the approach to intended use outlined in the NPRM, the Government could apply other provisions of Federal law; and that where there are gaps in existing legal provisions, FDA could seek specific product-based legislative changes.

(Response) We decline the comments' suggestions. Although it is true that the authorities mentioned in the comment enable FDA to keep some products containing pharmacological ingredients out of the food supply and dietary supplement marketplace, the comment overstates the reach of FDA's other authorities and overlooks the fact that simply being outside the dietary supplement or food definition does not make a product unlawful and subject to enforcement action. To establish jurisdiction over a product as a drug and remove it from the marketplace, or require the manufacturer to obtain FDA approval for the product before marketing it, FDA must be able to establish that the product is a drug based on evidence of its intended use. Thus, the regulatory tools the comment recommends are not a substitute for FDA's medical product authorities that include an intended use determination.

As the previous comment response explained, suggestions that FDA use other regulatory tools in place of



intended use would have a significant negative impact on public health. To protect consumers from dangerous products containing pharmacological ingredients like the cough suppressant in *United States v. Johnson* that caused several deaths, FDA intends to continue considering the full range of evidence relevant to determining intended use.

(Comment 5) One comment agreed with the NPRM that evidence of intended use could include conduct other than claims, but suggested that the rule clarify that the conduct must be promotional.

(Response) FDA declines this suggestion. FDA believes that the key issue in the intended use analysis is whether the evidence is “relevant,” which does not necessarily depend on whether there is evidence of “promotional” activity. The NPRM provided several examples to help inform the assessment of relevance. As the preamble explained, where a firm disseminates additional specific safety and warning information to healthcare providers to minimize the risk to patients receiving the drug for the unapproved use—an example of non-promotional speech—FDA would not consider such evidence to be relevant to intended use (see 85 FR 59718 at 59726). But the preamble provided other examples of evidence that would not necessarily be considered promotional that would still be relevant to intended use—such as designing a stent to be specifically sized for a use that is different from the purported use (see 85 FR 59718 at 59725). As another example, a factfinder might consider, as evidence of a new intended use, a spacer that the manufacturer claims can be used to elute one liquid, but is in fact designed with holes that are sized to elute a more viscous substance that contains a different active ingredient. Accordingly, FDA declines the suggestion to include “promotional” as a limiting principle for non-claims-based evidence that may be relevant to intended use.

This conclusion is consistent with recent case law. The case law describes the standard for determining intended use as “all relevant evidence.” This allows the fact finder to evaluate the facts of the specific case, which may involve a variety of situations and circumstances. For example, in *United States v. Carlson*, 810 F.3d 544 (8th Cir. 2016), defendants owned and/or worked at the Last Place on Earth, a head shop in Duluth, Minnesota, which sold synthetic drugs, such as synthetic marijuana. The products were labeled as incense, herbal incense, herbal potpourri, bath salts, etc., and also bore

the label statement “not for human consumption,” but defendants knew that customers purchased them to consume as drugs (see *id.* at 549; see also Amended Superseding Indictment, 12-cr-00305-DSD-LIB ¶ 9 (D. Minn. September 11, 2013)). The trial court instructed the jury that the product’s intended use “is what a reasonable person would conclude the manufacturer, seller or dispenser of the product intended the product to be used for, based on all of the relevant information” (see The Court’s Instructions to the Jury, 12-cr-00305-DSD-LIB at 58 (D. Minn. October 8, 2013)). The court explained that the jury could consider “any and all testimony and evidence,” whether or not the manufacturer, seller, or dispenser made contrary claims or no claims (see *id.* at 58–59). All of the defendants were convicted of distributing misbranded drugs in violation of the FD&C Act (see *Carlson*, 810 F.3d at 550).

In *United States v. Dessart*, 823 F.3d 395 (7th Cir. 2016), the defendant used a website to sell products containing human growth hormone (“HGH”), steroids, and the active ingredients in the prescription drugs VIAGRA (sildenafil), CIALIS (tadalafil), and LEVITRA (vardenafil). *Id.* at 398. The website said that the products were “for research only.” *Id.* The defendant was indicted on 23 counts of violating the FD&C Act. *Id.* at 399. The court instructed the jury: “[Y]ou should consider what a reasonable person would conclude the manufacturer or seller of the product intended the product to be used for, based on all of the relevant information. . . . You are not bound by any claims or statements made by the manufacturer or seller if there is other evidence concerning the use intended by the manufacturer or seller that conflicts with those claims or statements.” Jury Instructions, Case No. 12-CR-85 at 4–5 (E.D. Wis. June 19, 2014). The jury convicted on all counts. *Dessart*, 823 F.3d at 400.

In *United States v. 789 Cases of Latex Surgeons’ Gloves*, 799 F. Supp. 1275, 1294–1295 (D.P.R. 1992), the Government sought condemnation of surgeon’s gloves and their components, including cornstarch, stored in a rodent-infested facility. Although the product manufacturer argued that it did not intend for the gloves to be used in medical procedures, the court found that “[t]he circumstances surrounding the manufacture, distribution, and actual use of Plastic Material’s gloves present overwhelming evidence that claimant’s gloves are intended for use as—and therefore are—devices within the meaning of the Act”: *e.g.*, the sole

customer, the United States, purchased gloves only for medical use; and the cornstarch used to store the gloves was of a type used only with gloves intended for medical procedures.

In each of these cases, restricting relevant evidence to promotional claims and conduct could have led the factfinder to conclude that the products were outside of FDA’s jurisdiction.

(Comment 6) One comment asserted that the phrase “any relevant evidence” as used in the case law should be understood, under the statutory interpretation principle *ejusdem generis*, to refer only to evidence of promotional claims.

(Response) FDA disagrees. First, most obviously, principles of statutory construction are not typically applied to language in court decisions. Second, throughout this preamble, we have cited numerous examples where courts and FDA have considered evidence other than promotional claims to be relevant to establishing intended use.

#### *C. Comments and Responses Regarding the Design or Composition of an Article*

(Comment 7) Several comments stated that FDA should reconsider the proposed regulatory text identifying evidence about the “design or composition” of an article as a type of evidence relevant to establishing intended use. Some comments also asserted that the characteristics and design of a medical product that is approved, cleared, granted marketing authorization, or exempted from premarket notification do not determine intended use and that intended use does not depend on the design of the product. Some comments requested that FDA remove this phrase from the codified language describing the types of evidence relevant to determining a product’s intended uses.

(Response) We disagree with the comments and decline to remove “design or composition” from the codified language. As explained in the preamble, the revisions to the intended use regulations do not reflect a change in FDA’s policies and practices. Rather, the amendments to the intended use regulations are intended to describe the types of evidence relevant to determining a product’s intended use based on FDA’s current practices. The design and composition of an article are examples of the types of evidence that may be relevant when determining the article’s intended use. For example, FDA may consider the design or composition of a product, which includes product characteristics, when determining whether the product is “intended to affect the structure or any



function of the body” and therefore meets the device definition in section 201(h) of the FD&C Act (21 U.S.C. 321(h)). The addition of the phrase “design or composition” to the codified reflects FDA’s longstanding and current policy that these are relevant to intended use.

As discussed in the preamble to the NPRM, an example of a situation where design features have been found relevant to intended use include the design of a stent to be specifically sized for a use that is different from the purported use (see 85 FR 59718 at 59725). Another example can be found in *United States v. Caputo*, 517 F.3d 935 (7th Cir. 2008), where the Seventh Circuit upheld a conviction for misbranding under the FD&C Act where design features were part of the evidence of intended use. There, the district court recited evidence of the differences in design between two versions of the device that necessitated separate premarket review applications: “The larger sterilizer had different design and engineering characteristics: a six cubic foot chamber; a 5% peracetic acid mixture; different temperature, pressure, and gas flow rate; and a single, as opposed to multiple, use of the sterilant” (*United States v. Caputo*, 456 F. Supp. 2d 970, 973 (N.D. Ill. 2006), *aff’d in relevant part*, 517 F.3d 935 (7th Cir. 2008)). As another example, a factfinder might consider, as evidence of a new intended use, a spacer that the manufacturer claims can be used to elute one liquid, but is in fact designed with holes that are sized to elute a more viscous substance that contains a different active ingredient.

Another example where composition has been found relevant to intended use is *United States v. Undetermined Quantities . . . “Pets Smellfree,”* 22 F.3d 235 (10th Cir. 1994). In that case, the Government had seized and sought to condemn “Pets Smellfree” as an adulterated and misbranded drug. The product was promoted as an animal food additive to reduce pet odor when ingested. In determining that the product was a drug, the Tenth Circuit relied heavily on expert testimony about the physiological effects of a pharmacologically active ingredient, chlortetracycline, in reducing the level of bacteria in the animals’ digestive systems and oral cavities (see *id.* at 240). Other examples include *United States v. Zeyid*, 1:14-cr-0197, First Superseding Indictment (N.D. Ga. June 24, 2014) (see Ref. 2), where imported products labeled as “tea,” “coffee,” and “beauty products” contained active ingredients that were the same as those used in prescription drugs; FDA Warning Letter

to HelloCig Electronic Technology Co., Ltd. (Ref. 9), where undeclared active pharmaceutical ingredient was considered relevant to intended use; and FDA Warning Letter to INZ Distributors (Ref. 13), where presence of analogue of an erectile dysfunction drug was considered relevant to intended use.

(Comment 8) Some comments suggested that consideration of “design or composition of the article” as a type of evidence of intended use may inhibit technological advancements and discourage manufacturers from developing products that, based on their design, may be used for multiple uses.

(Response) FDA disagrees with these comments. We do not believe that considering a product’s design or composition to be relevant to the intended use of a product impedes technological advancements or discourages product development. As stated above, the relevance of a product’s design and composition to intended use is a part of FDA’s longstanding policy and has not hindered such improvements. For example, during premarket review of software, FDA may not always review a software device function that is included in the design but has been locked out, because it is not part of that specific premarket submission by the firm. If, however, the firm wants to unlock the software device function in the future, it must first obtain any necessary premarket clearance, marketing authorization or approval for the product with that function.

(Comment 9) One comment suggested that FDA should not seek enforcement after a product is approved, cleared, or granted marketing authorization solely based on that product’s design or characteristics, and another comment suggested that FDA should not assert a new intended use based solely on such features.

(Response) FDA applies applicable premarket and postmarket statutory and regulatory requirements to determine whether a product is legally marketed. FDA examines all relevant evidence in assessing compliance with such requirements. As previously noted, FDA may consider a product’s design or composition as one type of evidence relevant to the product’s intended use.

#### *D. Comments and Responses Regarding the First Amendment*

(Comment 10) One comment stated that because the rule identifies speech as potentially relevant to establishing intended use, and such speech may be truthful, the rule is “suspect” under the First Amendment. The comment

requested that FDA add specific statements to the codified language to address these concerns. Other comments similarly stated that the proposal does not adequately take into account the limitations on FDA’s authority to regulate truthful and non-misleading speech.

(Response) We disagree that the rule is vulnerable under the First Amendment. First, as noted in the preamble to the NPRM, we do not believe this rulemaking implicates the First Amendment. The intended use regulations describe evidence that may be relevant to establishing intended use; they do not in themselves directly regulate speech (85 FR 59718 at 59723). Indeed, the changes to the codified language proposed and finalized in this rulemaking do not directly involve speech: Whether, and to what extent, a factfinder may rely on product design, product composition, and knowledge as evidence of intended use, is not itself a First Amendment question, because speech will not typically be involved in such evidence. See 82 FR 2193 at 2207.

Second, in the regulatory regime under the FD&C Act and the PHS Act, intended use helps determine the marketing status for products that are potentially subject to those Acts, which products Congress has directed FDA to regulate in the interest of the public health. Part of the regulatory regime for medical products involves, for example, the review of appropriate labeling in the context of premarket review and postmarket regulatory surveillance. The categorical exclusion of all truthful speech from regulatory review would undermine FDA’s ability to promote and protect the public health through premarket review of medical products, including review of proposed labeling, and postmarket regulatory surveillance and actions.

For example, the Government prosecuted a clinic operator under the FD&C Act for injecting liquid silicone into the body to augment tissues such as the buttocks or breasts (Refs. 14 and 15). Silicone when used for industrial purposes would not fall within FDA’s jurisdiction. However, in this case, evidence that helped establish the intended use of the products included testimony of victims about the claims made to them by the defendant that the product would enhance the size of their buttocks. Those claims may have been truthful in the sense that they revealed one effect of the product. However, the injection of liquid silicone into the body for tissue augmentation can result in serious adverse health consequences, including hardening of tissue at the injection site, embolization, and even

death. FDA has not approved any liquid silicone products for injection to augment tissues anywhere in the body. Therefore, it was in the interest of public health for FDA to take action against the person responsible for the administration of these products, and such action was well within FDA's jurisdiction and permissible under the First Amendment.

There are many industries whose operations involve some amount of communication with the public. The fact that those communications may be truthful does not shield those industries' operations from Government regulation. "[I]t has never been deemed an abridgment of freedom of speech . . . to make a course of conduct illegal merely because the conduct was in part initiated, evidenced, or carried out by means of language, either spoken, written, or printed" (*Rumsfeld v. Forum for Academic and Institutional Rights, Inc.*, 547 U.S. 47, 62 (2006) (citation omitted)). And, as the Court recently confirmed, "the First Amendment does not prevent restrictions directed at commerce or conduct from imposing incidental burdens on speech" (*Barr v. Am. Ass'n of Political Consultants*, 140 S. Ct. 2335, 2347 (2020) (quoting *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 567 (2011))).

Thus, as we explained in the NPRM, courts have long upheld the premarket review requirements of the FD&C Act and the PHS Act, and the role of intended use within that framework, as necessary to promote and protect the public health and as fully consistent with the First Amendment (see 85 FR 59718 at 59723). More specifically, courts have held that, under the holding of *Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993), 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, e.g., *Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004); *Nicopure Labs, LLC v. FDA*, 944 F.3d 267, 283 (D.C. Cir. 2019); *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); see also *United States v. Article of Drug Designated B-Complex Cholinosis Capsules*, 362 F.2d 923, 927 (3d Cir. 1966); *United States v. General Nutrition, Inc.*, 638 F. Supp. 556, 562 (W.D.N.Y. 1986)). Indeed, reliance on

speech as evidence of intent is common in the law.<sup>2</sup>

Third, as also explained in the NPRM, even if this rulemaking or regulatory regime were appropriately subject to First Amendment review, FDA's consideration of speech as one type of evidence of intended use under its statutory and regulatory framework easily satisfies any applicable test. Under the *Central Hudson* framework, the threshold question is whether the speech is false or inherently or actually misleading or concerns unlawful activity—such speech may be prohibited (see *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n*, 447 U.S. 557 (1980); *In re R.M.J.*, 455 U.S. 191, 203 (1982); 44 *Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 497 n.7 (1996); 1–800–411–Pain Referral Serv., LLC v. Otto, 744 F.3d 1045, 1056 (8th Cir. 2014)). When commercial speech relates to an illegal activity, there is no First Amendment interest to weigh against the governmental interest supporting the regulation of commercial activity (*Pittsburgh Press Co. v. Human Relations Comm'n*, 413 U.S. 376, 389 (1973)). Regulated parties cannot be allowed to escape reasonable Government regulations by "bootstrap[ing] themselves into the heightened scrutiny of the First Amendment simply by infusing the prohibited conduct with some element of speech" (*Ford Motor Co. v. Tex. DOT*, 264 F.3d 493, 506–507 (5th Cir. Tex. 2001)).

For example, in *United States v. Caputo*, 517 F.3d 935 (7th Cir. 2008), the court found that it did not need to resolve the question of whether promotional claims for an approved medical device were protected by the First Amendment because defendants' product was not approved: "[t]here was no lawful activity for speech to promote" (id. at 941). In *United States v. Cole*, 84 F. Supp. 3d 1159 (D. Or. 2015), defendants distributed unapproved products with claims that they treated diseases, including Alzheimer's and HIV infection. The court rejected defendants' First

<sup>2</sup> See Reference 16 ("This pattern in the law—using intent as the predicate for regulation and then using speech as evidence of intent—is quite common, and not peculiar to pharmaceutical regulation. As early as 1888, the Supreme Court affirmed a state court criminal conviction for someone who manufactured an 'oleaginous substance' otherwise perfectly legal, except that he intended for it to be used as food, and thereby his manufacture of it fell under the purview of a state regulator. Similarly, a hollow piece of glass with a bowl on the end is illegal drug paraphernalia only if intended for such illicit uses. An automobile is not subject to regulation by the Federal Aviation Administration, unless it is 'intended to be used for flight in the air.'") (citations omitted).

Amendment defense, explaining that, because "[d]efendants' speech concerns an illegal activity—the introduction into interstate commerce of unapproved new drugs[,] . . . the First Amendment is not violated" (id. at 1166–67). In *United States v. LeBeau*, 2016 U.S. Dist. LEXIS 13612 (E.D. Wisc. February 3, 2016), the court similarly rejected defendant's First Amendment defense to a charge of distributing an unapproved new drug and explained that, because defendant's speech occurred while promoting and distributing a product that was intended for treatment of diseases and had not been approved by the FDA, his commercial speech did not concern lawful activity and did not pass step (1) of *Central Hudson* (see id. at 29). The Seventh Circuit affirmed, explaining that "[b]ecause LeBeau's statements promoted the unlawful sale of an unapproved drug, they were not entitled to protection" (*United States v. LeBeau*, 654 Fed. App'x 826, 831 (7th Cir. 2016)).

Even where the threshold step of *Central Hudson* does not apply, FDA's reliance on speech as evidence of intended use in the context of premarket review directly advances, and is appropriately tailored to achieve, substantial public health interests and therefore satisfies the remaining steps of the *Central Hudson* analysis. The medical products FDA regulates have the potential to adversely impact public health and safety. The premarket review requirements of the FD&C Act and the PHS Act require companies to conduct scientific research to determine the safety and effectiveness of medical products before they are marketed and 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. Accordingly, these premarket review provisions "do not ban manufacturers from making accurate claims" but instead "require them to substantiate such claims." *Nicopure Labs, LLC v. FDA*, 944 F.3d 267, 285 (D.C. Cir. 2019).

(Comment 11) One comment asserted that the NPRM failed to provide a meaningful explanation of how its consideration of speech as evidence of intended use comports with the *Central Hudson* test, particularly whether there are any less speech-restrictive alternatives with respect to speech regarding unapproved uses of approved products. The comment cites *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012) and criticizes the Government for not providing a sufficient explanation of its consideration of less-restrictive alternatives in the context of that lawsuit. Another commenter similarly

asserted that the NPRM did not adequately justify under *Central Hudson* the Government's policy regarding off-label use/promotion.

(Response) Again, as noted above and in the NPRM, we do not believe this rulemaking implicates the First Amendment, particularly given that the changes to the codified language proposed and finalized in this rulemaking do not directly involve speech. As further explained in the NPRM, "[b]ecause 'intended use' is only one element of an alleged violation of the FD&C Act, this rule does not itself implicate the First Amendment and does not attempt to resolve all First Amendment arguments that might be made by a firm in defending against an enforcement action under the FD&C Act." 85 FR 59798 at 59723 n.5. Nevertheless, in another proceeding, FDA has addressed in detail the issues raised by these comments (see Memorandum: Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products (January 2017) (Ref. 17)). Rather than repeat that analysis here, we summarize it briefly and incorporate the relevant portions of the document. The memorandum describes in detail the public health interests underlying and advanced by FDA's consideration of communications regarding unapproved uses of medical products that are approved, cleared, granted marketing authorization, or exempted from premarket notification as relevant to the premarket review requirements of the FD&C Act and PHS Act (see Ref. 17 at 3–16). As the memorandum explains, those requirements, among other things, motivate the development of scientific evidence that enables the reliable, population-level determination of the safety and efficacy of medical products for each intended use; require that the evidence be developed and independently reviewed before the products are marketed to the general public for each intended use; and require that the product bear labeling that identifies each medical use of the product that is approved, cleared, granted marketing authorization, or exempted from premarket notification and provides information for healthcare providers and patients on using the product safely and effectively for those uses that are approved, cleared, granted marketing authorization, or exempted from premarket notification. In the memorandum, FDA also examined alternative approaches suggested by the

court in *United States v. Caronia*, as well as by commentators (see *id.* at 26–34). FDA explained that, although many of these proposed approaches addressed one or more of the interests served by the premarket review requirements, FDA found that none of them integrated the complex mix of numerous interests at play and thus none of the proposed approaches best advanced those multiple interests (see *id.*).

(Comment 12) One comment asserted that the right of a manufacturer to convey truthful and non-misleading information is protected under *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002).

(Response) We disagree with the suggestion that *Western States* shields truthful and non-misleading speech from Government regulation. In that case, the Court applied the *Central Hudson* test to evaluate the regulation of the speech at issue, 535 U.S. at 368–77. In an analysis that broke no "new ground" (*id.* at 368), the Court explained that, in general, the Government should not restrict the communication of truthful and non-misleading information for the sole purpose of preventing members of the public from making bad decisions with the information (see *id.* at 374). However, that rationale is not applicable to this rulemaking because the premarket review requirements of the FD&C Act and PHS Act advance several different Government interests in protecting public health, as discussed above (see also Ref. 17).

(Comment 13) One comment asserted that the First Amendment protects not only the right to speak freely but also the right to hear and receive valuable information, and that this interest is particularly acute for the audience of physicians.

(Response) FDA has recognized that, under certain circumstances, both healthcare providers and patients may be interested in information about unapproved uses of products (see Ref. 17 at 17). In part because of this consideration, FDA has issued guidance documents describing circumstances in which the Agency does not intend to object to a firm's product communications or to view such communications as evidence of a new intended use (see 85 FR 59718 at 59723 & n.7). Nothing in this final rule reflects a change in FDA's policies and practices, as articulated in various guidance documents, regarding the types of firm communications that ordinarily would not, on their own, establish the firm's intent that a medical product that is approved, cleared, granted marketing authorization, or

exempted from premarket notification be used for an unapproved use. As discussed elsewhere in this preamble, FDA declines the suggestion to expand the scope of this rulemaking to additional subjects.

(Comment 14) One comment referenced for support a 1999 district court decision in a case brought by Washington Legal Foundation. Another comment referenced the same litigation and asserted that FDA is subject to a permanent injunction curtailing the Agency's authority to bar manufacturers from sharing peer-reviewed medical texts and journal articles about off-label uses of their FDA-approved products.

(Response) We believe these comments have little bearing on the current rulemaking. First, as explained in the NPRM, the proposed revisions to the intended use regulations do not reflect any change in FDA's policies and practices, as articulated in various guidance documents, regarding the types of firm communications to which the Agency does not intend to object or to view as evidence of a new intended use. Among the guidance documents describing these existing policies are several that relate to the distribution of peer-reviewed medical texts and journal articles (see 85 FR 59718 at 59723 & n.7). Second, with respect to the district court decision referenced in the comments, the D.C. Circuit "vacate[d] the district court's decisions and injunctions insofar as they declare the FDAMA and the CME Guidance unconstitutional" (see *Washington Legal Found. v. Henney*, 202 F.3d 331, 337 (D.C. Cir. 2000); see also *Washington Legal Found. v. Henney*, 128 F. Supp. 2d 11, 15 (D.D.C. 2000) (holding that "injunction has been wholly vacated by the Court of Appeals"); *id.* (holding that Court of Appeals "vacated all of this Court's previous constitutional rulings on the matter"); 65 FR 14286 (2000) (describing FDA's understanding of the outcome of the *Washington Legal Found.* litigation); Letter from Margaret M. Dotzel, Assoc. Commissioner for Policy, FDA to Daniel J. Popeo & Richard A. Samp, Wash. Legal Found., Docket No. 01P–0250 (January 28, 2002) (same)).

(Comment 15) Some comments asserted that content-based restrictions on commercial speech are subject to strict scrutiny or heightened scrutiny. One comment argued that *Sorrell v. IMS Health Inc.*, 564 U.S. 552 (2011), *Reed v. Town of Gilbert*, 135 S. Ct. 2218 (2015), *Matal v. Tam*, 137 S. Ct. 1744 (2017), and *Barr v. Am. Ass'n of Political Consultants*, 140 S. Ct. 2335 (2020) support the proposition that all content-based speech restrictions, even

those involving commercial speech, are subject to strict scrutiny, effectively overruling the *Central Hudson* and *Wisconsin v. Mitchell* lines of cases. Relying primarily on *Sorrell* and mentioning *Barr*, another comment asserted that FDA understated the constitutional limits on its authority in the NPRM. Another comment suggested that heightened scrutiny is warranted under *Sorrell* in the fields of medicine and public health.

(Response) We disagree. As we discussed in the NPRM, the Supreme Court in *Sorrell* suggested that content- and speaker-based restrictions would be subject to “heightened scrutiny,” but nevertheless continued to apply the “commercial speech inquiry” as outlined in *Central Hudson* (85 FR 59718 at 59724 n.11). Several courts of appeals have subsequently concluded that *Sorrell* did not overrule or fundamentally alter the *Central Hudson* analysis (see *Retail Digital Network, LLC v. Prieto*, 861 F.3d 839, 846 (9th Cir. 2017) (en banc) (*Sorrell* “did not mark a fundamental departure from *Central Hudson*’s four factor test, and *Central Hudson* continues to apply” to regulations of commercial speech, regardless of whether they are content based); *Missouri Broad. Ass’n v. Lacy*, 846 F.3d 295, 300 n.5 (8th Cir. 2017) (“The upshot [of *Sorrell*] is that when a court determines commercial speech restrictions are content- or speaker-based, it should then assess their constitutionality under *Central Hudson*.”) (quotation marks omitted; alteration in original); see also *Vugo, Inc. v. City of New York*, 931 F.3d 42, 50 (2d Cir. 2019) (“No Court of Appeals has concluded that *Sorrell* overturned *Central Hudson*. We agree with our sister circuits that have held that *Sorrell* leaves the *Central Hudson* regime in place, and accordingly we assess the constitutionality of the City’s ban under the *Central Hudson* standard.”), *cert. denied*, 140 S. Ct. 2717 (2020)).

In *Reed v. Town of Gilbert*, the Court applied strict scrutiny to content-based restrictions on non-commercial speech in sign ordinances. Although some of the language in the majority opinion in that case is broad, most lower courts have subsequently rejected arguments that *Reed* applies to the regulation of commercial speech (see, e.g., *Vugo, Inc. v. City of New York*, 931 F.3d 42, 49–50 & n.6 (2d Cir. 2019) (holding that *Central Hudson* still applies to commercial speech after *Reed* and *Sorrell*), *cert. denied*, 140 S. Ct. 2717 (2020); *Nationwide Biweekly Admin., Inc. v. Owen*, 873 F.3d 716, 732 (9th Cir. 2017) (“*Reed* did not relate to commercial speech . . . and therefore

did not have occasion to consider th[at] doctrine[.]”). Indeed, as one comment noted, in *Matal v. Tam*, a decision regarding content-based commercial speech issued after *Reed*, only one Justice advocated overruling *Central Hudson* in favor of strict scrutiny (137 S. Ct. 1744, 1769 (2017) (Thomas, J., concurring in part and concurring in the judgment)). No other Justice joined that opinion. While no First Amendment analysis garnered five votes in *Matal*, one four-Justice opinion applied *Central Hudson* (id. at 1764); the other four-Justice opinion stated that heightened scrutiny should be applied to viewpoint discrimination, but explained that viewpoint discrimination is an “egregious” subcategory of content-based regulation, and further noted that regulations regarding product labeling or consumer protection may be evaluated differently from the trademark matter at issue in that case (id. at 1766, 1768).

There was similarly no majority First Amendment analysis in *Barr v. Am. Ass’n of Political Consultants*, 140 S. Ct. 2335 (2020). There, the plurality opinion explained that strict scrutiny should be applied to a law that singled out a specific subject matter for differential treatment—permitting robocalls for collecting money owed to the Government while prohibiting robocalls for all other purposes (see id. at 2346). Similarly, Justice Gorsuch’s opinion emphasized that the statute under review favored certain voices while punishing others (see id. at 2364) (Gorsuch, concurring in the judgment in part and dissenting in part). In addition, the plurality opinion further circumscribed the scope of its holding: “The issue before us concerns only robocalls to cell phones. . . . Our decision is not intended to expand existing First Amendment doctrine or to otherwise affect traditional or ordinary economic regulation of commercial activity” (see id. at 2347; see also *Am. Hosp. Ass’n v. Azar*, 983 F.3d 528, 542 (D.C. Cir. 2020) (in upholding an HHS rule challenged in part on First Amendment grounds, the court distinguished *Barr* on the grounds that the restrictions in *Barr* involved political speech and the regulation at issue in *Am. Hosp. Ass’n* involved ordinary regulation of commercial activity)).

Accordingly, given that the Supreme Court has not overruled *Central Hudson* or *Wisconsin v. Mitchell* and given that the laws being reviewed in the cited cases were quite different from the premarket review provisions of the FD&C Act, we believe it would be wrong to conclude that the Supreme Court has

implicitly but sweepingly reversed these long-standing precedents to invalidate the regulatory regime under the FD&C Act. And even if some form of heightened scrutiny were applicable to reliance on speech as evidence of intended use, FDA believes that the public health necessity of the premarket review provisions discussed in this preamble, including its references, justifies and necessitates this regime under any standard.

(Comment 16) One comment asserted that scientific speech has been recognized as core speech that merits the highest degree of constitutional protection, citing *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51, 62 (D.D.C. 1998).

(Response) FDA agrees that, in certain contexts, scientific speech merits the highest degree of constitutional protection. However, the comment failed to note that the cited opinion determined that scientific speech will be evaluated under the First Amendment as commercial speech when a commercial entity seeks to distribute it in order to increase its sales of the product (see id. at 64–65).

(Comment 17) One comment urged FDA to follow the Sixth Circuit’s decision in *Int’l Outdoor, Inc. v. City of Troy*, 974 F.3d 690 (6th Cir. 2020), which the comment claimed held that all content-based speech restrictions are subject to strict scrutiny, even when the restrictions concern commercial speech.

(Response) FDA declines that suggestion for several reasons. First, *Int’l Outdoor*—like *Reed*—involved review of a sign ordinance, which does not raise the same complex regulatory and public health issues as premarket review under the FD&C Act and PHS Act. Second, a holding that strict scrutiny applies to all content-based commercial speech would run contrary to the weight of circuit court authority discussed above, including the Second Circuit’s recent decision in *Vugo, Inc.* confirming that *Central Hudson* continues to govern review of commercial speech (see 931 F.3d at 50). Third, the Sixth Circuit in *Int’l Outdoor* did not actually hold that strict scrutiny applies to all content-based commercial speech; the Sixth Circuit distinguished *Vugo* on the ground that the Second Circuit case involved only commercial speech, where *Int’l Outdoor* involved both core and commercial speech (see 974 F.3d at 705).

(Comment 18) One comment asserted that FDA should not continue to rely on *Wisconsin v. Mitchell* and its progeny because the district court in *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015) construed *United*

*States v. Caronia*, 703 F.3d 149 (2d Cir. 2012) to foreclose that position. Another comment similarly argued that the NPRM understated the meaning and impact of *Caronia*.

(Response) We disagree. As we explained in the NPRM, the Second Circuit has explicitly confirmed—contrary to the cited conclusion in *Amarin*—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). And the Second Circuit has more generally confirmed the continued viability of the *Wisconsin v. Mitchell* theory after *Caronia*, finding a First Amendment challenge to reliance on speech to show an element of violation “meritless” because “the speech is not ‘itself the proscribed conduct.’” *United States v. Pierce*, 785 F.3d 832, 841 (2d Cir. 2015) (quoting *Caronia*, 703 F.3d at 161). It is also noteworthy that the first comment did not cite any case other than *Amarin*, a district court decision on a motion for a preliminary injunction, in support of its position limiting the application of *Wisconsin v. Mitchell*. Indeed, decisions from other circuits issued after *Caronia* have upheld the application of *Wisconsin v. Mitchell* in the context of the premarket review requirements of the FD&C Act (see *Nicopure Labs, LLC v. FDA*, 944 F.3d 267, 283 (D.C. Cir. 2019); *United States v. Lebeau*, 654 Fed. App’x 826, 830–31 (7th Cir. 2016); *United States v. Facticeau*, 2020 U.S. Dist. LEXIS 167169 (D. Mass. September 14, 2020); *United States v. Cole*, 84 F. Supp. 3d 1159, 1166 (D. Or. 2015)).

#### E. Comments and Responses Regarding the Fifth Amendment

(Comment 19) Some comments questioned the constitutionality of the intended use regulations and asserted that the Fifth Amendment requires that the boundaries between permissible and impermissible communications be clearly drawn, particularly with respect to matters involving speech. One comment criticized FDA’s reliance on guidance documents to describe its enforcement policies in this regard.

(Response) While FDA agrees that laws must give a “person of ordinary intelligence a reasonable opportunity to know what is prohibited,” “meticulous specificity” is not required (see *Grayned v. City of Rockford*, 408 U.S. 104, 110 (1972)). The Supreme Court has recognized that laws may embody “flexibility and reasonable breadth” (see

*id.*) and officials implementing them may “exercise considerable discretion” (see *Ward v. Rock Against Racism*, 491 U.S. 781, 794 (1989)), without the laws being declared unconstitutional vague.

More specifically, the Supreme Court has held that “perfect clarity and precise guidance have never been required even of regulations that restrict expressive activity” (see *Ward*, 491 U.S. at 794 (citations omitted)). It is also well established that the use of an intent standard does not render a statute unconstitutionally vague (see *United States v. Williams*, 553 U.S. 285, 306 (2008); *Nat’l Ass’n of Manufacturers v. Taylor*, 582 F.3d 1, 26 (D.C. Cir. 2009) (“an intent standard is not per se vague, even in a statute regulating speech”)). Indeed, “absent special circumstances not present here, there is no reason to conclude that the ‘every day’ task of assessing intent is inherently vague [even] when protected speech is involved” (see *Taylor*, 582 F.3d at 27).

Moreover, courts have repeatedly rejected due process challenges to the FD&C Act as unconstitutionally vague or ambiguous. In *United States v. Hohensee*, 243 F.2d 367 (3d Cir. 1957), the Third Circuit rejected an unconstitutional vagueness challenge to provisions of the FD&C Act, which included the determination of intended use. In upholding the provisions, the court relied in part on the Supreme Court determination that the FD&C Act should “be given a liberal interpretation to effectuate its high purpose of protecting unwary consumers in vital matters of health” (see *id.* at 370; see also *United States v. Sullivan*, 332 U.S. 689, 695 (1948) (rejecting due process challenge to FD&C Act and finding no ambiguity in the misbranding language); *United States v. Caputo*, 517 F.3d 935, 941 (7th Cir. 2008) (rejecting argument that line between new and modified devices is too vague to be enforceable); *V.E. Irons v. United States*, 244 F.2d 34, 45 (First Cir. 1957) (rejecting as “untenable” the claim that the FD&C Act’s misdemeanor misbranding provisions are unconstitutionally vague and upholding misbranding conviction for distribution of vitamin and mineral products shown to be intended for use as drugs.); *United States v. General Nutrition, Inc.*, 638 F. Supp. 556, 564 (W.D.N.Y. 1986) (“The Act on numerous occasions has been upheld against vagueness challenges . . . and this Court is unaware of any case holding any provision of the Act void for vagueness in any circumstance.”) (citations omitted)).

The first FDA regulation describing how “intended use” is determined was

issued in 1952 (see 17 FR 6818, 6820 (1952) (Ref. 1)), and there have been only minor amendments since that time, including those being made through this rulemaking. Over nearly seven decades, medical product manufacturers have shown little difficulty in understanding how the regulations are applied. And, as noted in the NPRM, FDA has issued several guidance documents that describe circumstances in which the Agency does not intend to object to a firm’s product communications or to view such communications as evidence of a new intended use (85 FR 59718 at 59723). FDA issues these guidance documents to better inform stakeholders regarding its policies, and feedback from stakeholders has generally been positive. The NPRM also goes further than previous rulemakings related to these regulations in providing illustrative examples of types of evidence that would and would not be relevant to establishing intended use. Accordingly, we do not believe that the intended use regulations are unconstitutionally vague.

#### F. Comments and Responses Regarding Definitions

(Comment 20) Some comments suggested clarifying and defining the terms “intended use” and “indications for use” as these terms are used for devices in § 801.4. One comment suggested defining these terms by adopting definitions used in other FDA regulations and guidance documents. The comment also suggested clarifying the definitions of “intended use” and “indications for use” as part of a substantial equivalence determination for a device and distinguishing these terms from the intended use regulations for drugs.

(Response) FDA disagrees with these comments. The intended use regulations, including § 801.4, describe the types of evidence relevant to determining a product’s intended uses under the FD&C Act, the PHS Act, and FDA’s implementing regulations. The term “indications for use” is not used in this rulemaking and as such, FDA does not believe there is a need to define the term here. Further, FDA’s substantial equivalence determination during its review of a premarket notification is beyond the scope of this rulemaking.

(Comment 21) Several comments suggested revising § 801.4 to expressly include devices that are legally marketed without approval or clearance, such as devices exempt from premarket notification and granted marketing authorization. Some comments asserted that the terms “approved or cleared medical products” and “approved or

cleared medical uses” do not include such legally marketed devices and asked FDA to modify these terms to include 510(k)-exempt devices. One comment also suggested that FDA recognize how its review of drug and device labeling differ.

(Response) FDA agrees with adding language to § 801.4 to clarify that the regulation applies to devices that are exempt from premarket notification and devices that are granted marketing authorization through De Novo classification. We are adding the phrase “granted marketing authorization, or exempt from premarket notification” to the fourth sentence of § 801.4 to make this clarification.

FDA declines to compare FDA’s review of drug and device labeling because such comparison is beyond the scope of this rulemaking.

(Comment 22) Some comments suggested defining the terms “unapproved new use for an approved or cleared” and “unapproved use of an approved product” in the codified. Another comment asserted that these terms were not consistently used throughout the preamble.

(Response) We have included related terms and phrases in the definitions section of the preamble above to help clarify our use of these and similar phrases. We do not believe that it is necessary to include these definitions in the codified language.

(Comment 23) Some comments requested FDA expressly include laboratorians in the definition of “healthcare providers.”

(Response) The term “healthcare provider” includes a non-exhaustive list of individuals who are licensed or otherwise authorized by the State to prescribe, order, administer, or use medical products in a professional capacity. In some cases, this may include such licensed or otherwise State-authorized individuals with certain roles in a laboratory.

#### *G. Comments and Responses Regarding “Safe Harbors”*

(Comment 24) A number of comments suggested modifications to FDA policies that the comments sometimes refer to as “safe harbors” for certain kinds of medical product communications. Some comments suggested the establishment of a “safe harbor” for scientific exchange, whereby scientific exchange would be excluded from determinations of intended use. Other comments suggested the creation of “safe harbors” for other types of communications, including discussions with healthcare providers about investigational uses, discussions held in the course of

providing training or demonstrations to healthcare providers, market research about unapproved uses, and communications related to the collection of postmarket data. Another comment urged that FDA “codify in binding regulations its policies regarding manufacturer communication of scientific and medical information,” noting that guidance documents are not binding on enforcement authorities including the Department of Justice.

(Response) FDA welcomes and will continue to consider these comments related to “safe harbors.” However, the recommendations made in these comments go beyond the scope of this rulemaking, which is “to conform §§ 201.128 and 801.4 to reflect how the Agency currently applies them to drugs and devices,” 80 FR 57756 (2015). This rule, as proposed and as finalized, does not reflect a change in FDA’s policies and practices regarding the types of firm communications that ordinarily would not, on their own, establish a new intended use. Expanding the scope of this rule to codify FDA’s acknowledged “safe harbors” or to acknowledge additional “safe harbors,” as suggested in these comments, might warrant reproposing the rule to solicit additional input, unduly delaying the Agency’s clarification of its regulations on intended use. Therefore, while FDA will continue to consider the issues raised by these comments, the Agency declines the present suggestions to modify its acknowledged “safe harbors” or codify them in the intended use regulation.

With regard to the suggestion that the Agency establish a “safe harbor” for scientific exchange, whereby scientific exchange would be excluded from determinations of intended use: the Agency notes that if all scientific exchange were excluded from determinations of intended use, companies might have an incentive to create and promote new intended uses for marketed products based on incomplete or otherwise flawed data. That outcome would not serve the public health. At the same time, FDA recognizes the importance of scientific exchange, including information regarding unapproved uses of products that healthcare providers may choose to take into account when making professional judgments regarding the use of medical products that are approved, cleared, granted marketing authorization, or exempted from premarket notification. Balancing these public health considerations, some of which are in tension with each other, is a complex and important task. FDA believes this rulemaking, the purpose of which is to finalize amendments to the

intended use regulations, is not the appropriate forum to resolve separate questions relating to scientific exchange. As noted in the NPRM, FDA has issued several guidance documents that describe circumstances in which the Agency does not intend to object to a firm’s medical product communications or to view such communications as evidence of a new intended use. See 85 FR 59718 at 59723 n.7. This final rule does not disturb any of FDA’s acknowledged “safe harbors,” including those that encompass various types of scientific exchange. In addition, as discussed in the preamble to the proposed rule, a firm’s knowledge of off-label use plus safe-harbored communication would not, without more, be determinative of a new intended use. See 85 FR 59718 at 59725.

#### *H. Comments and Responses Regarding Examples*

(Comment 25) One comment requests that FDA clarify, consistent with the Government’s brief filed in *Par Pharmaceutical Inc. v. United States*, 1:11-cv-01820 (D.D.C.), that the example of “repeated proactive detailing” in the preamble to the proposed rule would not create a new intended use if the firm’s communications with the healthcare professionals are consistent with the approved labeling.

(Response) FDA declines the suggestion because FDA does not believe the proposed clarification is warranted. As explained in the preamble, the revisions to the intended use regulations do not reflect a change in FDA’s policies and practices, including as articulated in various guidance documents, regarding the types of firm communications that ordinarily would not, on their own, establish the firm’s intent that a medical product that is approved, cleared, granted marketing authorization, or exempted from premarket notification be used for an unapproved use (see 85 FR 59718 at 59723). The NPRM references guidance documents including FDA Guidance for Industry, “Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers,” June 2018 (see *id.* Ref. 5). As explained in that guidance, FDA does not intend to rely exclusively on a firm’s communication of information that is consistent with a medical product’s FDA-required labeling to establish a new intended use. The example in the NPRM, however, describes a circumstance involving a patient population that does not fall within the product’s approved population (see 85 FR 59718 at 59725) and, to the extent



the communication relates to a patient population outside the approved patient population reflected in the FDA-required labeling, the communication may not be considered consistent with the approved labeling. The *Par* brief cited in the comment confirms that a manufacturer's communication of information regarding an *approved use* to a physician whose patients do not fall within the product's approved population would not by itself establish a new intended use, but may be relevant together with other evidence in establishing the manufacturer's intent to distribute the product for an unapproved use (Ref. 3 at 17–18).

(Comment 26) Several comments requested modification to or clarification of the examples provided in section V.C. of the preamble to the proposed rule.

(Response) We decline to make the requested modifications to the examples. These examples were provided to illustrate evidence that, standing alone, would not be determinative of intended use, and they remain illustrative of that point. Although one comment suggested that the examples caused further confusion, most commenters indicated that the examples were helpful and encouraged FDA to offer additional examples. We continue to believe the examples provided in the preamble to the NPRM are helpful, and we are providing additional examples below. The list of examples in the proposed rule is not intended to be comprehensive or restrictive. Each scenario described in the preamble is fact-specific, and, under other circumstances or in other contexts, similar material may be evaluated differently.

(Comment 27) Several comments requested that FDA describe the intended use framework from the device industry perspective and provide additional device-specific examples.

(Response) The examples FDA provided in the preamble to the proposed rule were provided for illustrative purposes only and were not intended to be comprehensive or restrictive. In our responses to comments 7, 8, and 9 in this final rule preamble, we have provided additional examples of types of evidence<sup>3</sup> related

to product design and composition that may be relevant when determining a medical device's intended use. Those examples describe evidence that *may be relevant*, but is not necessarily determinative, to establishing intended use.

To further clarify this regulation as it applies to devices, we are providing here additional device-specific examples of types of evidence that may be relevant, but are not necessarily determinative, in establishing intended use. As with the examples in the preamble to the proposed rule, the following examples are fact-specific and are provided for illustrative purposes only.

- Marketing a medical device with a name that implies a use to affect a particular organ or system of the body. Example: “CardioCalm.”
- Designing a non-vascular stent with a coating clinically known to change calcification of blood vessels.
- Marketing a device that uses ultrasonic waves as a therapeutic massager, despite the fact that ultrasonic waves do not physically massage tissue but rather affect the underlying tissue through a sonic mechanism.

#### *I. Comments on Codified Text and FDA Responses*

(Comment 28) In the NPRM, FDA proposed to amend §§ 201.128 and 801.4 to provide that a firm would not be regarded as intending an unapproved new use for an approved drug or for a device approved, cleared, granted marketing authorization, or exempted from premarket notification based solely on that firm's knowledge that such drug or device was being prescribed or used by healthcare providers for such use. One commenter argued that FDA should delete “solely” from the regulations on intended use because this phrasing suggests that a firm's knowledge of unapproved use could be used in combination with other factors to determine the intended use of a product. Another commenter suggested that FDA should replace “solely” with a term that would clarify that such knowledge would be relevant only if such use is widespread and if a company's promotional activities are a primary reason for this widespread off-label use. This commenter also maintained that the final rule should be clear that only activities that are, at their core, promotional should be relevant for determining intended use.

(Response) FDA disagrees with these comments. The use of the word “solely”

in §§ 201.128 and 801.4 is intended to convey that FDA does not intend to consider a firm's knowledge that a healthcare provider has used or prescribed the firm's medical product that has been approved, cleared, granted marketing authorization, or is exempt from 510(k) for an unapproved use, *by itself*, as sufficient to establish intended use. The removal of the word “solely” from the regulation and the suggestion that FDA consider only activities that are fundamentally promotional in determining intended use would be inconsistent with the Agency's longstanding position that determining a product's intended use is a fact-specific inquiry and that FDA may consider all relevant sources of evidence. These sources of evidence may include a firm's knowledge that a healthcare provider has used or prescribed the firm's medical product that is approved, cleared, granted marketing authorization, or exempted from premarket notification for an unapproved use, and may include activities that are not strictly promotional in nature. In short, direct promotion of the use is not necessary to establish intended use.

(Comment 29) One comment asked FDA to change “article” to “device” throughout § 801.4.

(Response) FDA disagrees with this suggestion. The use of the term “article” in §§ 201.128 and 801.4 is consistent with the use of that term in section 201 of the FD&C Act.

(Comment 30) A comment suggested deleting the phrase “or used” from the fourth sentence of § 801.4, asserting that a healthcare provider's use is not “under the control of the firm.”

(Response) FDA disagrees with the comment's suggestion because, although the healthcare provider's use is not under the firm's control, what may be relevant to intended use is the firm's knowledge that the article is being used by the healthcare provider. As discussed above, both legislative history and the case law support reliance on actual use by healthcare providers as relevant to intended use. See, e.g., *United States v. An Article of Device Toftness Radiation Detector*, 731 F.2d 1253, 1257 (7th Cir. 1984); *United States v. 22 Rectangular or Cylindrical Finished Devices*, 714 F. Supp. 1159, 1165 (D. Utah 1989); *United States v. Device Labeled “Cameron Spitler Amblyo-Syntonizer,”* 261 F. Supp. 243, 245 (D. Neb. 1966); H.R. Rep. No. 853, 94th Cong., 2d Sess. 14 (1976). However, a firm's knowledge that healthcare providers are prescribing or using its product that has been approved, cleared, granted marketing authorization, or is 510(k)-exempt for an

<sup>3</sup> As described in the preamble to the proposed rule, these types of evidence include express claims and representations; implied claims; product characteristics and design; and the circumstances of the product's sale or distribution (see 85 FR 59718 at 59725). In fulfilling its mission to protect the public health, FDA will evaluate the individual and unique circumstances of each case in determining a product's intended use. In some cases, a single piece of evidence may be dispositive of a product's

intended use. In others, several elements combined may establish a product's intended use.



unapproved use would not, by itself, automatically trigger an obligation to provide labeling for that unapproved use.

(Comment 31) One comment suggested that FDA explain how § 801.4 applies to modifications of 510(k)-cleared devices.

(Response) FDA declines to adopt this suggestion because it is beyond the scope of this rulemaking.

(Comment 32) One comment stated that section 513(i)(1)(E) of the FD&C Act (21 U.S.C. 360c(i)(1)(E)) constrains how FDA “responds to an intended use not reflected in device labeling when reviewing a 510(k)” and that FDA “cannot require that the company obtain clearance or approval of another potential unapproved use.” The comment also suggested FDA disassociate intended use regulations for devices from drugs and add a reference to section 513(i)(1)(E) of the FD&C Act in the codified text of § 801.4.

(Response) FDA’s application of section 513(i)(1)(E) of the FD&C Act is beyond the scope of this rulemaking.

#### *J. Comments Recommending That FDA Expand the Scope of This Rulemaking*

(Comment 33) A number of comments urged FDA to expand this rulemaking beyond the scope of the proposed rule. For example, one comment urged FDA to “complete its long-promised ‘comprehensive review’ of regulations to assess alignment with constitutional and statutory requirements.” Another comment proposed that FDA adopt a regulatory approach to manufacturer speech consistent with the “Principles on Responsible Sharing of Truthful and NonMisleading Information About Medicines with Health Care Professionals and Payers” developed by Pharmaceutical Research and Manufacturers of America and the Biotechnology Innovation Organization.

(Response) Although FDA welcomes the submission of ideas regarding a broader list of suggested policy changes, we decline to adopt the suggestions in these comments because they are beyond the scope of this rulemaking. Expanding the scope of this rule as suggested in these comments would potentially delay FDA’s clarification of its regulations on intended use. FDA has been engaged in a continuing review of regulations and policies regarding communications with healthcare providers and payors (and other similar entities with knowledge and expertise in healthcare economic analysis) regarding medical products, and has taken other initiatives as part of that effort.

(Comment 34) One comment contended that the regulatory requirements for premarket approval and authorization are too burdensome so that it is unreasonable to require that manufacturers conduct studies and submit applications for every intended use.

(Response) This comment also raises issues that are different from and beyond the scope of this rulemaking. To the extent this comment is suggesting that the best way to address complex questions concerning premarket authorization is through limiting the scope of intended use, we disagree that this is an appropriate tool.

(Comment 35) One comment requested that FDA acknowledge that healthcare providers may prescribe and use approved/cleared medical products for unapproved uses when they judge that the unapproved use is medically appropriate for their patients and that manufacturers are not required to confirm the nature of a healthcare provider’s planned use for an approved medical product before distributing such product to the healthcare provider.

(Response) Healthcare providers prescribe or use medical products that are approved, cleared, granted marketing authorization, or exempted from premarket notification for unapproved uses based on their medical judgment regarding any potential benefits and risks of the unapproved use for their individual patients.<sup>4</sup> In these limited circumstances, FDA’s longstanding position is that the Agency does not consider a firm’s knowledge that a healthcare provider has used or prescribed its medical product that is approved, cleared, granted marketing authorization, or exempted from premarket notification for an unapproved use, by itself, as sufficient to establish the intended use element of a prohibited act based on failing to meet applicable premarket requirements for that use or failing to provide adequate directions for use.<sup>5</sup>

<sup>4</sup> FDA generally does not seek to interfere with the exercise of the professional judgment of healthcare providers in prescribing or using, 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). Although 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 (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) and result in the drug being deemed “unsafe” and therefore adulterated under sections 512 and 501(a)(5) (21 U.S.C. 351(a)(5)) of the FD&C Act.

<sup>5</sup> See 21 U.S.C. 331(d), 351(f), 352(f)(1), 355(a). The position described in the text does not apply to products that are not already legally marketed as

## **VI. Effective Date**

This final rule will become effective 30 days after the date of its publication in the **Federal Register**.

## **VII. Economic Analysis of Impacts**

### *A. Introduction and Summary*

#### **1. Introduction**

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). 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. We cannot predict how many companies may revise labeling, advertising, or other materials, or otherwise modify their behavior, following issuance of this rule. However, this rule would merely clarify, but not change, the types of evidence relevant to determining manufacturers’ intended use of products. Because the rule would not extend FDA’s authority to additional products or impose any additional requirements on currently regulated products, we expect the rule will impose negligible costs, if any. As a result, 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 proposing “any rule that includes any Federal

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.

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 \$158 million, using the most current (2020) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

## 2. Summary of Costs and Benefits

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

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

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

TABLE 1—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF FINAL RULE

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered	
Benefits:							
Annualized Monetized \$millions/year .....	.....	.....	.....	.....	7	.....	
Annualized Quantified .....	.....	.....	.....	.....	3	.....	
Qualitative .....	.....	.....	.....	.....	7	.....	
	.....	.....	.....	.....	3	.....	
	Clarification of intended use interpretation and application						
Costs:							
Annualized Monetized \$millions/year .....	.....	.....	.....	.....	7	.....	
Annualized Quantified .....	.....	.....	.....	.....	3	.....	
Qualitative .....	.....	.....	.....	.....	7	.....	
	.....	.....	.....	.....	3	.....	
	Negligible costs, if any						
Transfers:							
Federal Annualized Monetized \$millions/year .....	.....	.....	.....	.....	7	.....	
	.....	.....	.....	.....	3	.....	
From/To .....	From:			To:			
Other Annualized Monetized \$millions/year .....	.....	.....	.....	.....	7	.....	
	.....	.....	.....	.....	3	.....	
From/To .....	From:			To:			
Effects:							
State, Local or Tribal Government: None.							
Small Business: None.							
Wages: None.							
Growth: None.							

## 3. Comments on the Preliminary Economic Analysis of Impacts and Our Response

We did not receive any comments on the Preliminary Economic Analysis of Impacts.

## 4. Summary of Changes

We have made no significant changes from the Preliminary Economic Analysis of Impacts.

### B. Final Economic Analysis of Impacts

#### 1. Background

This rule clarifies FDA’s longstanding position that the intended use of a drug or device product can be based on any relevant source of evidence by describing types of evidence relevant to the intended use of a product and types

of evidence that, standing alone, are not determinative of intended use.

One important clarification involves a manufacturer’s knowledge of unapproved uses of its approved product. Current versions of §§ 201.128 and 801.4 specify that a manufacturer of a drug (§ 201.128) or device (§ 801.4) must include adequate labeling if it knows its product is used for an unapproved purpose. The September 2015 proposed rule (80 FR 57756 at 57764) removed the sentence regarding the requirement to provide adequate labeling if a firm knows its product is being used for an unapproved use. The amended January 2017 final rule (82 FR 2193 at 2217) was intended to clarify FDA’s position by requiring manufacturers to include adequate labeling “if the totality of the evidence

establishes that a manufacturer objectively intends that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than ones for which it is approved (if any).”

In the **Federal Register** of February 7, 2017 (82 FR 9501), FDA delayed the effective date of the January 2017 final rule until March 2017. In February 2017, various industry organizations filed a petition raising concerns with the January 2017 final rule, requesting reconsideration and a stay. The petition requested that FDA reconsider the amendments to the “intended use” regulations and issue a new final rule that, with respect to the intended use regulations at §§ 201.128 and 801.4, reverted to the language of the September 2015 proposed rule. The

petition also requested that FDA indefinitely stay the rule because petitioners argued that the final rule was issued in violation of the fair notice requirement under the Administrative Procedure Act and that the “totality of the evidence” language in the 2017 final rule was a new and unsupported legal standard.

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

2. Benefits of the Final Rule

The final rule clarifies FDA’s existing interpretation of the determination of the intended use of drugs and devices. This clarification should reduce manufacturer and stakeholder uncertainty regarding the scenarios in which specific types of evidence may or

may not show a product is intended for a drug or device use. The removal of the final sentence in §§ 201.128 and 801.4 and the inclusion of new clarifying clauses (“provided, however, that a firm would not be regarded as intending an unapproved new use for [a medical product that is approved, cleared, granted marketing authorization, or exempted from premarket notification] based solely on that firm’s knowledge that such [product] was being prescribed or used by health care providers for such use”) resolve questions about whether manufacturers need to think about developing an action plan or strategy related to a potential new intended use of their medical products that are approved, cleared, granted marketing authorization, or exempted from premarket notification simply because a manufacturer has knowledge of unapproved uses of these products by third parties. We believe this clarification is the benefit of the final rule.

3. Costs of the Final Rule

The final rule is not expected to impose significant additional costs on manufacturers and distributors of FDA-regulated products. The final rule does not extend FDA’s regulatory authority to any new or additional products, nor

does the rule change the current approach to evaluating intended use or impose any additional requirements on manufacturers or distributors. We do not have any reason to believe firms will change their marketing or operating procedures as a result of this rule. We do not have evidence that this final rule would impose costs on currently marketed products.

C. Final Small Entity Analysis

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

TABLE 2—SMALL BUSINESS ADMINISTRATION SIZE STANDARDS FOR AFFECTED INDUSTRIES

NAICS code	Industry description	Small business threshold
312230 .....	Tobacco Manufacturing .....	Fewer than 1,500 Employees.
325411 .....	Medicinal and Botanical Manufacturing .....	Fewer than 1,000 Employees.
325412 .....	Pharmaceutical Preparation Manufacturing .....	Fewer than 1,250 Employees.
325413 .....	In-vitro Diagnostic Substance Manufacturing .....	Fewer than 1,250 Employees.
325414 .....	Biological Product (except Diagnostic) Manufacturing.	Fewer than 1,250 Employees.
339112 .....	Surgical and Medical Instrument Manufacturing	Fewer than 1,000 Employees.
339113 .....	Surgical Appliance and Supplies Manufacturing	Fewer than 750 Employees.
339114 .....	Dental Equipment and Supplies Manufacturing	Fewer than 750 Employees.
339115 .....	Ophthalmic Goods Manufacturing .....	Fewer than 1,000 Employees.
339116 .....	Dental Laboratories .....	Fewer than 500 Employees.

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h), (i), 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.

IX. Paperwork Reduction Act of 1995

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. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive

order and, consequently, a federalism summary impact statement is not required.

XI. Consultation and Coordination With Indian Tribal Governments

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.

## XII. References

The following references are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <https://www.regulations.gov>. FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

1. Regulations for the Enforcement of the Federal Food, Drug, and Cosmetic Act, 17 FR 6818, 6820 (1952).
2. U.S. Department of Justice, U.S. Attorney's Office, Northern District of Georgia, "Five Defendants Charged With Illegally Importing Male Enhancement Products," May 29, 2014 (available at <https://www.justice.gov/usao-ndga/pr/five-defendants-charged-illegally-importing-male-enhancement-products>).
3. Defendants' Memorandum in Support of Motion to Dismiss or for Summary Judgment and in Opposition to Motion for Preliminary Injunction at 8, *Par Pharmaceutical Inc. v. United States*, 1:11-cv-01820 (D.D.C. December 23, 2011).
4. Defendants' Memorandum of Points and Authorities in Support of Motion to Dismiss or for Summary Judgment at 8–9 n.5, *Allergan Inc. v. United States*, 1:09-cv-01879–JDB, (D.D.C. January 11, 2010).
5. Plaintiff's Motion for Summary Judgment at 20–26, *United States v. Undetermined Quantities of Articles of Drug, Street Drug Alternatives, Identified in Attachment A, et al.*, Civil No. AW–00–1687 (D. Md. January 12, 2001).
6. Government Trial Memorandum at 6, *United States v. Teiman*, Criminal No: 7:00CR00054 (W.D. Va. September 29, 2000).
7. Letter from Steven B. Barber, District Director, Cincinnati District, FDA to Marc C. Sanchez, Esq., Mood and Mind, LLC, at 9–10 (April 6, 2017).
8. Letter from Margaret M. Dotzel, Assoc. Commissioner for Policy, FDA to Daniel J. Popeo and Richard A. Samp, Wash. Legal Found., at 6, Docket No. 01P–0250 (January 28, 2020).
9. Letter from Ann Simoneau, J.D., Director, Office of Compliance and Enforcement, Center for Tobacco Products and Donald D. Ashley, J.D., Director, Office of Compliance, Center for Drug Evaluation and Research, FDA to HelloCig Electronic Technology Co., Ltd (October 11, 2018).
10. Letter from Ramon A. Hernandez, Director, San Juan District Office and

Program Division Director, Office of Human and Animal Food Operations, Division IV East, FDA, to Ricardo Mayo-Alvarez, Duy Drugs, Inc. (August 28, 2018).

11. Letter from Daniel Solis, Director, Import Operations Branch, Los Angeles District to Carol A. Pratt, K&L Gates LLP (December 3, 2012).
12. Letter from Alonza E. Cruse, District Director, Los Angeles District, FDA to Richard Carieri, Lifetech Resources Labs Inc. (April 18, 2011).
13. Letter from Ronald M. Pace, District Director, New York District, FDA to Peter Erikh, INZ Distributors, Inc. (August 23, 2010).
14. U.S. Department of Justice, "December 2, 2016: Woman Arrested for Injecting Adulterated Liquid Silicone," accessed December 23, 2020, <https://www.justice.gov/usao-pr/pr/woman-arrested-injecting-adulterated-liquid-silicone>.
15. U.S. Department of Justice, 2018, "March 2, 2018: Woman Sentenced for Injecting Adulterated Liquid Silicone," accessed December 23, 2020, <https://www.justice.gov/usao-pr/pr/woman-sentenced-injecting-adulterated-liquid-silicone>.
16. Robertson, C.T. "When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment," 94 B.U.L. REV. 545, 549–50 (2014).
17. Memorandum: Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products (January 2017) (available at <https://www.regulations.gov/document?D=FDA-2016-N-1149-0040>).

## List of Subjects

### 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

### 21 CFR Part 801

Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, 21 CFR parts 201 and 801 are amended as follows:

## PART 201—LABELING

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

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

- 2. Revise § 201.128 to read as follows:

### § 201.128 Meaning of intended uses.

The words *intended uses* or words of similar import in §§ 201.5, 201.115, 201.117, 201.119, 201.120, 201.122, and 1100.5 of this chapter refer to the objective intent of the persons legally

responsible for the labeling of an article (or their representatives). The intent may be shown by such persons' expressions, the design or composition of the article, or by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. Objective intent may be shown, for example, by circumstances in which the article is, with the knowledge of such persons or their representatives, offered or used for a purpose for which it is neither labeled nor advertised; provided, however, that a firm would not be regarded as intending an unapproved new use for an approved drug based solely on that firm's knowledge that such drug was being prescribed or used by health care providers for such use. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he or she received the article, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses.

## PART 801—LABELING

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

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

- 4. Revise § 801.4 to read as follows:

### § 801.4 Meaning of intended uses.

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

on that firm's knowledge that such device was being prescribed or used by health care providers for such use. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he or she received the article, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses.

Dated: July 14, 2021.

**Janet Woodcock,**

*Acting Commissioner of Food and Drugs.*

Dated: July 22, 2021.

**Xavier Becerra,**

*Secretary, Department of Health and Human Services.*

[FR Doc. 2021-15980 Filed 7-30-21; 8:45 am]

**BILLING CODE 4164-01-P**

## DEPARTMENT OF HOMELAND SECURITY

### Coast Guard

#### 33 CFR Part 165

[Docket Number USCG-2021-0480]

RIN 1625-AA00

#### **Safety Zone; Lake of the Ozarks, Mile Markers 7, 10.5, 13, 16, 22, 26, 34, and 42, Lake of the Ozarks, MO**

**AGENCY:** Coast Guard, DHS.

**ACTION:** Temporary final rule.

**SUMMARY:** The Coast Guard is establishing temporary safety zones in all navigable waters extending 420 feet in all directions around fireworks barges at eight different locations on the Lake of the Ozarks. These safety zones are needed to protect personnel, vessels, and the marine environment from potential hazards created by the fireworks displays. Entry of vessels or persons into these zones is prohibited unless specifically authorized by the Captain of the Port Sector Upper Mississippi River or a designated representative.

**DATES:** This rule is effective on August 10, 2021 at 10 p.m. to 10:30 p.m.

**ADDRESSES:** To view documents mentioned in this preamble as being available in the docket, go to <https://www.regulations.gov>, type USCG-2021-0480 in the search box and click "Search." Next, in the Document Type column, select "Supporting & Related Material."

**FOR FURTHER INFORMATION CONTACT:** If you have questions on this rule, call or email Lieutenant Commander Stephanie Moore, Sector Upper Mississippi River Waterways Management Division, U.S. Coast Guard; telephone 314-269-2560, email [Stephanie.R.Moore@uscg.mil](mailto:Stephanie.R.Moore@uscg.mil).

#### **SUPPLEMENTARY INFORMATION:**

##### **I. Table of Abbreviations**

CFR Code of Federal Regulations  
DHS Department of Homeland Security  
FR Federal Register  
NPRM Notice of proposed rulemaking  
§ Section  
U.S.C. United States Code

##### **II. Background Information and Regulatory History**

The Coast Guard is issuing this temporary rule without prior notice and opportunity to comment pursuant to authority under section 4(a) of the Administrative Procedure Act (APA) (5 U.S.C. 553(b)). This provision authorizes an agency to issue a rule without prior notice and opportunity to comment when the agency for good cause finds that those procedures are "impracticable, unnecessary, or contrary to the public interest." Under 5 U.S.C. 553(b)(B), the Coast Guard finds that good cause exists for not publishing a notice of proposed rulemaking (NPRM) with respect to this rule because it is impracticable. We must establish this safety zone by August 10, 2021 and lack sufficient time to provide a reasonable comment period and then consider those comments before issuing the rule.

Under 5 U.S.C. 553(d)(3), the Coast Guard finds that good cause exists for making this rule effective less than 30 days after publication in the **Federal Register**. Delaying the effective date of this rule would be contrary to the public interest because immediate action is needed to respond to the potential safety hazards associated with the fireworks displays on August 10, 2021.

##### **III. Legal Authority and Need for Rule**

The Coast Guard is issuing this rule under authority in 46 U.S.C. 70034 (previously 33 U.S.C. 1231). The Captain of the Port Sector Upper Mississippi River (COTP) has determined that potential hazards associated with the fireworks displays on August 10, 2021 will be a safety concern for anyone on the Lake of the Ozarks at the designated launch locations. This rule resulted from a marine event notification stating that there will be fireworks displays to celebrate a bicentennial birthday on the Lake of the Ozarks. This rule is needed to protect personnel, vessels, and the marine environment in the navigable

waters within the safety zone before, during, and after the fireworks display.

##### **IV. Discussion of the Rule**

This rule establishes safety zones on August 10, 2021 from 10 p.m. until 10:30 p.m. The safety zones will be located on all navigable waters extending 420 feet in all directions around fireworks barges at the following locations on the Lake of the Ozarks at (1) mile marker 7 (38 12'35.20" N 92 45'02.57" W), (2) mile marker 10.5 (38 01'21.93" N 92 47'38.93" W), (3) mile marker 13 (38 11'01.86" N 92 41'19.32" W), (4) mile marker 16 (38 08'54.89" N 92 38'29.53" W), (5) mile marker 22 (38 08'54.89" N 92 41'18.95" W), (6) mile marker 26 (38 07'25.22" N 92 42'58.65" W), (7) mile marker 34 (38 07'25.22" N 92 47'34.59" W) and (8) mile marker 42 (38 08'55" N 92 52'23.30" W). The duration of these zones is intended to protect personnel, vessels, and the marine environment in these navigable waters before, during, and after the fireworks displays. No vessel or person will be permitted to enter the safety zones without obtaining permission from the COTP or a designated representative. A designated representative is a commissioned, warrant, or petty officer of the U.S. Coast Guard assigned to units under the operational control of USCG Sector Upper Mississippi River. The COTP or a designated representative will inform the public of the enforcement date and times for these safety zones, as well as any emergent safety concerns that may delay the enforcement of the zones.

##### **V. Regulatory Analyses**

We developed this rule after considering numerous statutes and Executive orders related to rulemaking. Below we summarize our analyses based on a number of these statutes and Executive orders, and we discuss First Amendment rights of protestors.

###### **A. Regulatory Planning and Review**

Executive Orders 12866 and 13563 direct agencies to assess the costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits. This rule has not been designated a "significant regulatory action," under Executive Order 12866. Accordingly, this rule has not been reviewed by the Office of Management and Budget (OMB).

This regulatory action determination is based on size, location, and duration of the temporary safety zones. This action involves fireworks displays at multiple designated locations on the