Appendix 3—Statement of Commissioner Dan M. Berkovitz

I support issuing for public comments two notices of proposed rulemaking to improve the operation of the CFTC's Margin Rule.[1] The Margin Rule requires certain swap dealers (''SDs'') and major swap participants (''MSPs'') to post and collect initial and variation margin for uncleared swaps.[2] The Margin Rule is critical to mitigating risks in the financial system that might otherwise arise from uncleared swaps. I support a strong Margin Rule, and I look forward to public comments on the proposals, including whether certain elements of the proposals could increase risk to the financial system and how the final rule should address such risks.

The proposals address: (1) The definition of material swap exposure (''MSE'') and an alternative method for calculating initial margin (''the MSE and Initial Margin Proposal''); and (2) the application of the minimum transfer amount (''MTA'') for initial and variation margin (''the MTA Proposal''). They build on frameworks developed by the Basel Committee on Banking Supervision and International Organization of Securities Commissions (''BCBS/IOSCO''),[3] existing CFTC staff no-action letters, and recommendations made to the CFTC's Global Markets Advisory Committee (''GMAC'').[4] I thank Commissioner Stump for her leadership of the GMAC and her work to bring these issues forward for the Commission's consideration.

Today's proposed amendments to the Margin Rule could help promote liquidity and competition in swaps markets by allowing the counterparties of certain end-users to rely on the initial margin calculations of the more sophisticated SDs with whom they enter into transactions designed to manage their risks, subject to safeguards. They would also address practical challenges in the Commission's MTA rules that arise when an entity such as a pension plan or endowment retains asset managers to invest multiple separately managed accounts (''SMAs''). Similar operational issues are addressed with respect to initial and variation margin MTA calculations.

These operational and other benefits justify publishing the MSE and Initial Margin Proposal and the MTA Proposal in the **Federal Register** for public comment. However, I am concerned that specific aspects of each of these proposed rules could weaken the Margin Rule and increase risk by creating a potentially larger pool of uncollateralized, uncleared swaps exposure. My support for finalizing these proposals will depend on how the potential increased risks are addressed.

One potential risk in the MSE and Initial Margin Proposal arises from amending the definition of MSE to align it with the BCBS/IOSCO framework.[5] One element of the proposal would amend the calculation of the average daily aggregate notional amount (''AANA'') of swaps. The proposed rule would greatly reduce the number of days used in the calculation, reducing it from an average of all business days in a three month period to the average of the last business day in each month of a three month period.[6] The result would be that a value now calculated across approximately 60+ data points (*i.e.,* business days) would be confined to only three data points, and could potentially become less representative of an entity's true AANA and swaps exposure. Month-end trading adjustments could greatly skew the AANA average for an entity.

When the Commission adopted the Margin Rule in 2016, it rejected the MSE calculation approach now under renewed consideration. U.S. prudential regulators also declined to follow the BCBS/IOSCO framework in this regard. The Commission noted in 2016 that an entity could ''window dress'' its exposure and artificially reduce its AANA during the measurement period.[7] Even in the absence of window dressing, there are also concerns that short-dated swaps, including intra-month natural gas and electricity swaps, may not be captured in a month-end calculation window. While the MSE and Initial Margin Proposal offers some analysis addressing these issues, it may be difficult to extrapolate market participants' future behavior based on current regulatory frameworks. I look forward to public comment on these issues.

The MSE and Initial Margin Proposal and the MTA Proposal each raise additional concerns that merit public scrutiny and comment. The MTA Proposal, for example, would permit a minimum transfer amount of $50,000 for each SMA of a counterparty. In the event of more than 10 SMAs with a single counterparty (each with an MTA of $50,000), the proposal would functionally displace the existing aggregate limit of $500,000 on a particular counterparty's uncollateralized risk for uncleared swaps. The proposal would also state that if certain entities agree to have separate MTAs for initial and variation margin, the respective amounts of MTA must be reflected in their required margin documentation. Under certain scenarios, these separate MTAs could result in the exchange of less total margin than if initial and variation margin were aggregated.

The MSE and Initial Margin Proposal and the MTA Proposal both articulate rationales why the Commission preliminarily believes that the risks summarized above, and others noted in the proposals, may not materialize. The Commission's experience with relevant staff no-action letters may also appear to lessen concerns around the proposals. While each item standing on its own may not be a significant concern, the collective impact of the proposed rules may be a reduction in the strong protections afforded by the 2016 Margin Rule—and an increase in risk to the U.S. financial system. The Commission must resist the allure of apparently small, apparently incremental, changes that, taken together, dilute the comprehensive risk framework for uncleared swaps.

I look forward to public comments and to continued deliberation on what changes to the MSE and Initial Margin Proposal and the MTA Proposal are appropriate. I thank Commissioner Stump, our fellow Commissioners, and staff of the Division of Swap Dealer and Intermediary Oversight for their extensive engagement with my office on these proposals.

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[1] Margin Requirements for Uncleared Swaps for Swap Dealers and Major Swap Participants, 81 FR 636 (Jan. 6, 2016) (''Margin Rule'').

[2] *See also* Commodity Exchange Act (''CEA'') section 4s(e). The CEA, as amended by the Dodd-Frank Act, requires the Commission to adopt rules for minimum initial and variation margin for uncleared swaps entered into by SDs and MSPs for which there is no prudential regulator. Although addressed in the rules, there are currently no registered MSPs.

[3] BCBS/IOSCO, Margin requirements for non-centrally cleared derivatives (July 2019), *https://www.bis.org/bcbs/publ/d475.pdf.* The BCBS/IOSCO framework was originally promulgated in 2013 and later revised in 2015.

[4] Recommendations to Improve Scoping and Implementation of Initial Margin Requirements for Non-Cleared Swaps, Report to the CFTC's Global Markets Advisory Committee by the Subcommittee on Margin Requirements for Non-Cleared Swaps, April 2020, *https://www.cftc.gov/media/3886/GMAC_051920MarginSubcommitteeReport/download.*

[5] 17 CFR 23.151.

[6] Existing Commission regulation 23.151 specifies June, July, and August of the prior year as the relevant calculation months. The proposed rule would amend this to March, April, and May of the current year. The proposed rule would also amend the calculation date from January 1 to September 1. These amendments would be consistent with the BCBS/IOSCO framework.

[7] *See* CFTC Margin Rule, 81 FR at 645.

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: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing to amend its medical product ''intended use'' regulations. This action, if finalized, will amend 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 an approved or cleared medical product is intended for a new use. This action will also repeal and replace the portions of a final rule issued on January 9, 2017, that never became effective. This action is intended to provide direction and

clarity to regulated industry and other stakeholders.

DATES: Submit either electronic or written comments on the proposed rule by October 23, 2020.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before October 23, 2020. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of October 23, 2020. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

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

Instructions: All submissions received must include the Docket No. FDA–2015–N–2002 for ''Amendments to Regulations Regarding 'Intended Uses'.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

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

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I. Executive Summary

A. Purpose of the Proposed Rule

FDA is proposing 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, including whether a product meets the definition of a drug or device and whether an approved or cleared medical product is intended for a new use. The Agency issued a proposed rule in 2015 and a final rule in 2017 revising the language of these 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 final rule and reopened the docket to invite public comment. A number of comments submitted during the reopening raised questions and

concerns about the amendments. On March 18, 2018, 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 is proposing to repeal the portions of the final rule issued on January 9, 2017, that never became effective and to issue a new rule to provide more clarity regarding the types of evidence that are relevant in determining a product's intended uses. This action is intended to provide direction and clarity to regulated industry and other stakeholders.

B. Summary of the Major Provisions of the Proposed Rule

FDA proposes to amend 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 an approved or cleared medical product is intended for a new use. Some firms have expressed concern that the last sentence of § 201.128 could be read to mean that a firm's mere knowledge of an unapproved use of its approved drug product automatically triggers requirements for new labeling that in turn renders distribution of that approved product unlawful without approval of a supplemental application. Section 801.4 contains comparable language regarding medical devices. The Agency is proposing to delete the last sentence of §§ 201.128 and 801.4 and to insert a new clause in the body of the regulations (''provided, however, that a firm would not be regarded as intending an unapproved new use for an [approved or cleared medical product] based solely on that firm's knowledge that such [product] was being prescribed or used by health care providers for such use'') to clarify that a firm's knowledge that health care providers are prescribing or using its approved or cleared medical product for an unapproved use would not, by itself, automatically trigger obligations for the firm to provide labeling for that unapproved use. In addition, FDA proposes amending the text of §§ 201.128 and 801.4 to provide additional clarification regarding the types of evidence that are relevant to determining a product's intended uses. Additional clarification is provided in the preamble.

FDA is also proposing to insert in §§ 201.128 and 801.4 a reference to § 1100.5 (21 CFR 1100.5), which describes when a product made or derived from tobacco that is intended for human consumption will be subject to regulation as a drug, device, or combination product. This change is being proposed to clarify the interplay between the drug and device intended use regulations and FDA's regulations governing products that are made or derived from tobacco and intended for human consumption.

C. Legal Authority

Among the provisions that provide authority for this proposed 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 proposed 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 an approved or cleared medical product is intended for a new use. We do not have evidence that the proposed rule would impose costs on currently marketed products.

II. Meaning of Certain Terms in This Preamble

As used in this preamble, the following terms have the meanings noted below.[1]

Term	Meaning
Approved or cleared medical product.	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 (including devices that are granted marketing authorization or are exempt from premarket notification).
Approved or cleared medical use.	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.
Health care 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.
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 or cleared (as that term is described above) by FDA for any medical use, and which must be approved or cleared 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 an approved product.	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.

[1] Nothing in this table is intended to construe terms in the FD&C Act, the PHS Act, or FDA's implementing regulations, nor does the information in the table otherwise affect discussions outside the context of this preamble.

III. Background

A. Introduction and History of the Rulemaking

In the **Federal Register** of September 25, 2015 (80 FR 57756), FDA issued a proposed rule entitled ''Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding 'Intended Uses.''' Among other proposals, that 2015 notice of proposed rulemaking proposed certain changes to FDA's existing regulations describing the types of evidence relevant to determining a product's intended uses (see §§ 201.128 (drugs) and 801.4 (devices)). These amendments were intended to clarify FDA's existing interpretation and application of these regulations (see 80 FR 57756 at 57761). Specifically, the amendments were intended to clarify that a firm would not be regarded as intending an unapproved new use for an approved product based solely on that firm's knowledge that its product was being prescribed or used by health care providers for such use (see 80 FR 57756 at 57761). FDA proposed to delete the last sentence of the intended use regulations (§§ 201.128 and 801.4) to provide this clarification, in addition to some other changes.

Before FDA's issuance of the proposed rule in 2015, some firms had expressed concern with the last sentence of § 201.128. (Refs. 1 to 3). That sentence states that if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug that accords with such other uses. (§ 801.4 contains comparable language.) These firms asserted (with some variations in the argument) that this sentence could be read to mean that whenever a manufacturer knew that its approved drug was being prescribed or used by a health care provider for an unapproved use, the manufacturer would be required to alter the labeling of a drug to provide adequate directions for such unapproved use. Firms further asserted that this addition to FDA-approved labeling would transform the drug into a new drug that cannot be sold without first obtaining approval of a supplemental new drug application pursuant to sections 201(p) and 505(a) (21 U.S.C. 355(a)) of the FD&C Act.[2] Firms asserted that, based on this, under the last sentence of § 201.128, a manufacturer's mere knowledge of an unapproved use of its approved drug automatically triggers requirements for new labeling that in turn renders distribution of that approved product unlawful without approval of a supplemental application.

In the 2015 proposed rule, the proposed deletion of the last sentence of §§ 201.128 and 801.4 was intended to clarify the following: When a firm is distributing an approved or cleared medical product, evidence that the firm knows that health care providers are prescribing or using that approved or cleared medical product for an unapproved use would not, by itself, automatically trigger obligations for the firm to provide labeling for the uses for which the health care providers are prescribing or using the product. FDA's clarification of its position and proposed deletion of the last sentence of these regulations in the proposed rule was not intended to suggest that FDA sought to otherwise change the scope of evidence relevant to intended use.

At the time the final rule issued in January 2017, FDA believed that the goals described in the preceding paragraph would be better achieved by amending the last sentence of each intended use regulation, rather than by deleting the sentences (see 82 FR 2193 at 2206). In the preamble to that final rule, FDA explained that the revised language was intended to achieve the goal described in the proposed rule by amending the last sentence so that it no longer suggested that a firm's mere knowledge that its approved or cleared product is being prescribed or used for an unapproved use would, on its own, trigger the requirement to provide adequate labeling (see 82 FR 2193 at 2206). The revised sentence was also intended to reflect FDA's longstanding position, discussed in both the preambles to the 2015 proposed rule and the 2017 final rule, that the intended use of a product can be evaluated based on ''any relevant source of evidence,'' including a variety of direct and circumstantial evidence (see 82 FR 2193 at 2206). The text of the final rule used the phrase ''the totality of the evidence'' to accomplish these goals (see 82 FR 2193 at 2206).

The final rule was published with an initial effective date of February 8, 2017, which was delayed until March 21, 2017, in accordance with the memorandum of January 20, 2017, from the Assistant to the President and Chief of Staff, entitled ''Regulatory Freeze Pending Review'' (Ref. 4). On February 8, 2017, various industry organizations filed a petition (Docket No. FDA–2015–N–2002–1977) raising concerns with the January 2017 final rule. In March 2017, we further delayed the effective date of the final rule and reopened the docket to invite additional public comment. In March 2018, we delayed the effective date of the intended use amendments until further notice to allow for further consideration of the substantive issues raised in the comments received. Having considered these issues, FDA is proposing to repeal the intended use amendments contained in the final rule issued on January 9, 2017, that never took effect, and to issue a new rule that would replace the January 2017 rule in amending the intended use regulations to further clarify the types of evidence relevant to determining a product's intended uses. The January 2017 final rule also added a new regulation (§ 1100.5) to title 21 of the CFR (see 82 FR 2193 at 2217). That regulation became effective on March 19, 2018. Its status is unaffected by this proposed rule.

B. How Intended Use Is Evaluated

FDA's longstanding position is that, in evaluating a product's intended use, any relevant source of evidence may be considered. This position is unchanged and has solid support in the case law (see, *e.g., United States* v. *Storage Spaces Designated Nos. 8 and 49,* 777 F.2d 1363, 1366 (9th Cir. 1985); *Action on Smoking and Health* v. *Harris,* 655 F.2d 236, 239 (D.C. Cir. 1980); *Nat'l Nutritional Foods Ass'n* v. *Mathews,* 557 F.2d 325, 334 (2d Cir. 1977); *United States* v. *Article of 216 Cartoned Bottles, ''Sudden Change,''* 409 F.2d 734, 739 (2d Cir. 1969); *V.E. Irons, Inc.* v. *United States,* 244 F.2d 34, 44 (1st Cir. 1957); *United States* v. *LeBeau,* 2016 U.S. Dist. LEXIS 13612, *27, 2016 WL 447612 (E.D. Wis. Feb. 3, 2016), *aff'd,* 654 Fed. App'x 826, 831 (7th Cir. 2016); *United States* v. *Schraud,* 2007 U.S. Dist. LEXIS 89231, *5 (E.D. Mo. Dec. 4, 2007); *Hanson* v. *United States,* 417 F. Supp. 30, 35 (D. Minn.), *aff'd,* 540 F.2d 947 (8th Cir. 1976)). Evidence of intended use may include, but is not limited to, the product's labeling, promotional claims, and advertising. For example, any claim or statement made by or on behalf of a firm that explicitly or implicitly promotes a product for a particular use may be taken into account.

A firm's subjective claims of intent, however, are not necessarily determinative of a product's intended use. Objective evidence of the firm's intent, which can include a variety of direct and circumstantial evidence, is also relevant, particularly when it

[2] The same argument could apply with respect to new animal drugs (see sections 201(v) and 512(a) (21 U.S.C. 360b(a) of the FD&C Act).

contradicts the firm's claims. Indeed, courts have rejected the proposition that evidence of intended use is limited to labeling or other claims by a manufacturer concerning a device or drug (see *Nat'l Nutritional Foods Ass'n* v. *Mathews,* 557 F.2d 325, 334 (2d Cir. 1977) (''In determining whether an article is a 'drug' because of an intended therapeutic use, the FDA is not bound by the manufacturer's subjective claims of intent but can find actual therapeutic intent on the basis of objective evidence. Such intent also may be derived or inferred from labeling, promotional material, advertising, and any other relevant source.'') (internal citation and quotations omitted); *United States* v. *Travia,* 180 F. Supp. 2d 115, 119 (D.D.C. 2001) (''Labeling is not exclusive evidence of the sellers' intent. Rather, as the very language quoted by the defendants themselves states, 'it is well established ''that the intended use of a product, within the meaning of the [FD&C Act], is determined from its label, accompanying labeling, promotional claims, advertising, *and any other relevant source*'''. . . . even *consumer* intent could be relevant, so long as it was pertinent to demonstrating the seller's intent . . . [I]f the government's allegations are true, the sellers did not need to label or advertise their product, as the environment provided the necessary information between buyer and seller. In this context, therefore, the fact that there was no labeling may actually bolster the evidence of an intent to sell a mind-altering article without a prescription—that is, a misbranded drug.'') (citations omitted); *United States* v. *Vascular Solutions, Inc.,* 181 F. Supp. 3d 342, 347 (W.D. Tex. 2016) (''[T]hough [21 CFR] 801.4 indeed says that 'objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives,' nowhere does the regulation state that such statements or claims cannot be used to show objective intent unless they were published to the marketplace.''); see also *United States* v. *Storage Spaces Designated Nos. 8 and 49,* 777 F.2d 1363, 1366 n.5 (9th Cir. 1985) (concluding that products innocuously labeled as ''incense'' and ''not for drug use'' were in fact drugs when the ''overall circumstances'' demonstrated vendor's intent that products be used as cocaine substitutes); *United States* v. *An Article of Device Toftness Radiation Detector,* 731 F.2d 1253, 1257 (7th Cir. 1984) (intended use established in part by witness testimony that device had been used to treat patients, together with other evidence regarding a training program and financial arrangements offered by the defendant); *United States* v. *Undetermined Quantities of an Article of Drug Labeled as* ''*Exachol,*'' 716 F. Supp. 787, 791 (S.D.N.Y. 1989) (explaining that ''FDA is not bound by the vendor's subjective claims of intent'' and that ''[a]n article intended to be used as a drug will be regulated as a drug . . . even if the products [sic] labelling states that it is not a drug'')).

Courts have repeatedly held that intended use is determined by looking to all relevant evidence, including statements and circumstances surrounding the manufacture and distribution of a product (see, *e.g., United States* v. *Article of 216 Cartoned Bottles . . .*''*Sudden Change,*'' 409 F.2d 734, 739 (2d Cir. 1969) (''It is well settled that the intended use of a product may be determined from its label, accompanying labeling, promotional material, advertising and any other relevant source.'') (citations omitted); *V.E. Irons, Inc.* v. *United States,* 244 F.2d 34, 44 (1st Cir. 1957) (observing that a court is ''free to look to all relevant sources in order to ascertain what is the 'intended use' of a drug'')). As explained by one court: ''Whether a product's intended use makes it a device depends, in part, on the manufacturer's *objective* intent in promoting and selling the product. All of the circumstances surrounding the promotion and sale of the product constitute the 'intent.' It is not enough for the manufacturer to merely *say* that he or she did not 'intend' to sell a particular product as a device. Rather, the actual circumstances surrounding the product's sale . . . determine the 'intended' use of the product as a device under the Act'' (*United States* v. *789 Cases, More or Less, of Latex Surgeons' Gloves,* 799 F. Supp. 1275, 1285 (D.P.R.1992) (emphasis in original) (internal citations omitted)).

As FDA has previously stated, however, the Agency would not regard a firm as intending an unapproved use for its approved medical product based solely on the firm's knowledge that such product was being prescribed or used by health care providers for such use (80 FR 57756 at 57757; 82 FR 2193 at 2206–2207). Health care providers sometimes prescribe or use approved or cleared medical products for unapproved uses when they judge that the unapproved use is medically appropriate for their individual patients.[3] In such circumstances, FDA does not consider a firm's knowledge that a health care provider has prescribed or used its approved or cleared medical product for an unapproved use to be sufficient by itself to establish the intended use element of a prohibited act related to the lack of premarket approval or clearance of that use or the lack of adequate directions for use.[4] Instead, FDA examines all relevant evidence, which could include, in combination with other facts, a firm's knowledge that health care providers are prescribing or using its approved or cleared medical product for an unapproved use, to determine whether there is sufficient evidence to establish a new intended use.

Some comments submitted in the earlier rulemaking presented views regarding First Amendment considerations relating to how a product's intended use is established. However, treating knowledge as a category of evidence that may be considered as evidence of intended use does not, in itself, implicate the First Amendment. Knowledge and speech are not coextensive. A variety of direct and circumstantial evidence can establish a person's knowledge; a person's speech can be one source—but is not the only source—of evidence of that person's knowledge. The proposed amendments are not intended to address specific concerns arising under the First Amendment, but instead seek to address an ambiguity in the language of the regulations and to conform that language to FDA's existing policy. Accordingly, and consistent with the statutory framework and purposes, FDA

[3] FDA generally does not seek to interfere with the exercise of the professional judgment of health care 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 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).

[4] See 21 U.S.C. 331(a), 331(d), 351(f), 352(f)(1), 355(a), 360b. That position does not apply to products that are not already legally marketed as medical products for at least one use. Similarly, nothing in this regulation or preamble is intended to interfere with 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 a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services under section 505 [of the FD&C Act] and pursuant to the order of a physician.'' Furthermore, Congress or the Agency could issue other product-specific or product class-specific provisions that recognize knowledge as sufficient evidence of a particular element of a prohibited act.

is clarifying in this rulemaking that while knowledge can be within the types of evidence that are relevant to establishing intended use, a firm's knowledge that its approved or cleared medical product is being prescribed or used by health care providers for an unapproved use would not be relied upon as the sole evidence of a new intended use.

Some comments submitted in the earlier rulemaking suggested that FDA should rely exclusively on firms' claims to establish intended use. This narrow view of intended use would not only create a loophole for firms that would enable them to evade FDA oversight of the marketing of approved or cleared medical products for unapproved uses, but would also open the door to the marketing of products that are unapproved for any medical use—all to the detriment of the public health. As courts have recognized, ''[s]elf-serving labels cannot be allowed to mask the vendor's true intent as indicated by the overall circumstances'' (*United States* v. *Storage Spaces Designated Nos. 8 and 49,* 777 F.2d 1363, 1366 n.5 (9th Cir. 1985)). As one court explained, ''[a] disease claim made with a wink and a nudge is still a disease claim. To hold otherwise would create an 'obviously wide loophole' that would defeat the 'high purpose of the Act to protect consumers' '' (*United States* v. *Cole,* 84 F. Supp. 3d 1159, 1166 (D. Or. 2015) (citation omitted)). Examples where the government has relied on evidence other than express claims to establish intended use include situations where products contained a pharmacological ingredient such as the active ingredient from approved erectile dysfunction and hair-loss products, albuterol, or steroids, but were labeled as herbal supplements, leather cleaner, incense, potpourri, bath salts, or ''for research purposes only.'' Similar examples for devices include: (1) Products that are labeled as laser pointers or hyperbaric chambers but, based on other objective evidence, are actually intended by the manufacturer or the distributor to treat serious conditions such as cancer, diabetes, multiple sclerosis, human immunodeficiency virus (HIV), and autism; and (2) a product with a reservoir that is cleared for use with a saline solution to moisten tissue but, based on other objective evidence, is actually intended to deliver a drug (*e.g.,* steroids) to the tissue. The government has also considered firms' directions to their sales forces in determining intended use. Thus, in addition to claims, FDA may also take into account any circumstances surrounding the distribution of the product or the context in which it is sold (see *An Article of Device Toftness Radiation Detector,* 731 F.2d at 1257; see also *United States* v. *Travia,* 180 F. Supp. 2d 115, 119 (D.D.C. 2001)). Considering evidence other than express claims often ensures that FDA is able to pursue firms that attempt to evade FDA medical product regulation by avoiding making express claims about their products.

This rule, if finalized, would be consistent with the First Amendment. First, the rule is limited in scope. It describes evidence that *may be relevant* to establishing intended use, but it does not dictate that certain evidence *will be determinative* of intended use in an individual case.[5] Second, nothing in this proposed rule, if finalized, would affect any exclusion explicitly provided by statute or regulation from the definitions of *drug* or *device*.[6] Third, the proposed revisions to the intended use regulations do not reflect 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 an approved or cleared medical product be used for an unapproved use.[7] If a firm's communication is consistent with the recommended practices described in FDA guidance, such a communication, on its own, would not be evidence of a new intended use.[8]

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,[9] as necessary to promote and protect the public health and as fully consistent with the First Amendment. Courts have held that the government's reliance on speech as evidence of intended use under the FD&C Act does not infringe the right of free speech under the First Amendment based on Supreme Court precedent establishing that ''[t]he First Amendment . . . does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent'' (*Wisconsin* v. *Mitchell,* 508 U.S. 476, 489 (1993)). The D.C. Circuit applied that precedent in the context of the FD&C Act and held that ''th[e] use of speech to infer intent, which in turn renders an otherwise permissible act unlawful, is constitutionally valid'' and hence ''it is constitutionally permissible for the FDA to use speech [by the manufacturer] . . . to infer intent for purposes of determining that [the manufacturer's] proposed sale . . . would constitute the forbidden sale of an unapproved drug'' (*Whitaker* v. *Thompson,* 353 F.3d 947, 953 (D.C. Cir. 2004); see also *Nicopure Labs, LLC* v. *FDA,* 944 F.3d 267, 283 (D.C. Cir. 2019) (''Just as the government may consider speech that markets a copper bracelet as an arthritis cure . . . in order to subject the item to appropriate regulation, so, too, the FDA may rely on e-cigarette labeling and other marketing claims in order to subject e-cigarettes to appropriate regulation''); *Flytenow, Inc.* v. *FAA,* 808 F.3d 882, 894 (D.C. Cir. 2015) (upholding ''us[e of] speech (postings on Flytenow.com) as evidence that pilots are offering service that exceeds the limits of their certifications''). Likewise, although the Second Circuit's decision in *United States* v. *Caronia,* 703 F.3d 149 (2d Cir. 2012), ''construe[d] the misbranding provisions of the FDCA as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs'' and concluded that ''the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-

[5] Because ''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.

[6] For example, section 201(g)(1) of the FD&C Act contains exclusions from the drug definition for two types of labeling claims that would otherwise subject a product to regulation as a drug: (1) Structure/function claims and certain related claims in the labeling of dietary supplements, when made in accordance with section 403(r)(6) of the FD&C Act; (2) health claims in the labeling of a conventional food or dietary supplement, when made in accordance with section 403(r)(3) or (r)(5)(D) of the FD&C Act, as applicable.

[7] The Agency has issued several final 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 (sometimes referred to as ''safe harbors'') (Refs. 5 to 7). The Agency has also recognized ''safe harbors'' in draft guidance documents (Refs. 8 and 9). When final, these documents will represent FDA's current thinking on these topics. The Agency invites comment on whether any elements of these guidances warrant codification in the regulations.

[8] As noted elsewhere in this preamble, this is not to suggest that these communications must be excluded from consideration altogether. For example, if there is other evidence of a new intended use for a product, such communications may be evaluated in assessing the classification and regulatory status of the product.

[9] It should be noted that intended use is relevant in contexts other than premarket approval and clearance. For example, FDA evaluates intended use in determining whether research studies involving human subjects involve the administration of a drug and must be conducted under an investigational new drug application (see 21 CFR part 312).

approved drug,'' *id.* at 168–169,[10] the decision ''left open the government's ability to prove misbranding on a theory that promotional speech provides evidence that a drug is intended for a use that is not included on the drug's FDA-approved label.'' *United States ex rel. Polansky* v. *Pfizer,* Inc., 822 F.3d 613 n.2 (2d Cir. 2016).

In addition, FDA's consideration of speech as one type of evidence of intended use under its statutory and regulatory framework directly advances, and is appropriately tailored to achieve, substantial public health interests relevant to analyses under *Central Hudson Gas & Electric Corp.* v. *Public Service Comm'n,* 447 U.S. 557, 563–64 (1980).[11] 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.[12] Accordingly, these premarket review provisions ''do[] not ban manufacturers from making accurate claims'' but instead ''require[] them to substantiate such claims.'' *Nicopure Labs, LLC,* 944 F.3d at 285.

IV. Legal Authority

Among the statutory provisions that provide authority for this proposed 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 (21 U.S.C. 262). 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) 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'' (21 U.S.C. 262), and section 351(j) of the PHS Act provides that the requirements of the FD&C Act apply to biological products (21 U.S.C. 262). 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. Description of the Proposed Rule

A. Introduction

FDA is issuing this proposed rule to clarify the types of evidence relevant to determining a product's intended uses, including determining whether a product meets the definitions of drug or device and whether an approved or cleared medical product is intended for a new use. The proposed rule would insert in §§ 201.128 and 801.4 a reference to § 1100.5, to clarify the interplay between the medical product intended use regulations and the regulation that describes when a product made or derived from tobacco that is intended for human consumption will be subject to regulation as a drug, device, or combination product. The Agency also proposes to delete the final sentence of §§ 201.128 and 801.4 and to insert a new clause in the body of the regulations (''provided, however, that a firm would not be regarded as intending an unapproved new use for an [approved or cleared medical product] based solely on that firm's knowledge that such [product] was being prescribed or used by health care providers for such use'') to clarify that a firm would not be regarded as intending an unapproved use for its approved product based solely on that firm's knowledge that its product was being prescribed or used by health care providers for such use. FDA is also proposing additional changes to the codified text to clarify and reinforce that intended use can be based on any relevant source of evidence, including a variety of direct and circumstantial evidence.

In the following sections, FDA provides several examples of types of evidence relevant to establishing intended use. These examples are provided for illustrative purposes only and are not intended to be comprehensive or restrictive. 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.

B. Types of Evidence Relevant to Establishing Intended Use

1. Express Claims and Representations

In determining a product's intended use, any claim or statement made by or on behalf of a firm that explicitly represents a product for a particular use is relevant. This can include, but is not limited to, labeling claims and representations (whether made in required labeling or labeling that is optional or promotional), advertising matter, and oral or written statements by persons responsible for the labeling, or their representatives.

2. Implied Claims

Any claim or statement made by or on behalf of a firm that implicitly represents a product for a particular use is also relevant to intended use. Examples of such implicit claims may include the following:

- Suggestive product names such as Chronix, Shroomz, or e-Cialis;

[10] This holding was ''limited to FDA-approved drugs for which off-label use is not prohibited.'' 709 F.3d at 168–69. Any constitutional interest in such speech does not extend to speech promoting the introduction of a wholly unapproved medical product into interstate commerce, which is an illegal activity. See *United States* v. *Caputo*, 517 F.3d 935, 939–40 (7th Cir. 2008); *United States* v. *Cole*, 84F. Supp. 3d 1159, 1166–67 (D.Or. 2015).

[11] In *Sorrell* v. *IMS Health Inc.,* 564 U.S. 552, 565 (2011), the Supreme Court explained that content-based commercial speech restrictions may be subject to ''heightened judicial scrutiny.'' 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, 2020 U.S. LEXIS 2437 (Apr. 27, 2020).

[12] See Eguale, T., D.L. Buckeridge, A. Verma, et al., ''Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population,'' *Journal of American Medical Association Internal Medicine,* 176(1):55–63, 2016 (summarizing study across cohort of 46,000 patients, and concluding that unapproved use of prescription drugs is associated with adverse drug events, particularly where those uses lack strong scientific evidence in the form of at least one randomized controlled trial) (Ref. 10).

• Statements that imply an intended use, such as ''For best results use approximately 30–45 minutes prior to engaging in sexual intercourse''; or

• Representations that the product contains a particular ingredient to imply a physiological effect, such as the inclusion of ''aspirin'' or ''sildenafil'' in the ingredient list.

3. Product Characteristics and Design

The characteristics of the product and its design are relevant to establishing intended use. Examples of such evidence include the following:

• The known physiological effects (medical or recreational) of a product that is unapproved for any medical use (for example, products containing an active pharmaceutical ingredient (API) [13] or an analogue of an API or controlled substance).

○ Example scenarios might include dried herbs treated with synthetic tetrahydrocannabinol (THC), or coffee containing sildenafil.

• The known use (recreational or medical) of a product that is unapproved for any medical use.

○ Example scenarios might include 2,4-Dinitrophenol (DNP) being used for weight loss, herbal products being used for pain management, or a product being used for a medical purpose for which it provides no known benefit (*e.g.,* Laetrile (amygdalin) for cancer).

• The product's design or technical features.

○ Example scenarios might include a stent that is specifically sized for a use that is different from the purported use; a suture delivery device with a snare loop sized for a specific procedure that is different from the purported use; a device that includes software with a diagnostic function when the purported use does not include diagnosis; or products that purport to remove only the stratum corneum (outer layer of the skin) but that are actually designed to penetrate below the stratum corneum into the living layers of the skin.

4. Circumstances of the Sale or Distribution

The types of evidence relevant to establishing intended use also include circumstances surrounding the distribution of the product and the context in which it is sold, including the following:

• To whom and for whom the products are offered, such as a firm's repeated proactive detailing and delivery of large amounts of complimentary product samples to a health care provider whose patient population does not fall within the product's approved population.

• Circumstances and context surrounding the sale, such as balloons containing laughing gas (nitrous oxide) being sold outside a rock concert, or the repackaging of bulk product into smaller plastic bags and using personal, not business, emails and addresses for communications and deliveries.

C. Examples of Evidence That, Standing Alone, Are Not Determinative of Intended Use

1. Knowledge, Alone or in the Context of ''Safe Harbors,'' of Health Care Providers Prescribing or Using an Approved Product for an Unapproved Use

As discussed previously, a firm will not be regarded as intending an unapproved use of an approved product based solely on that firm's knowledge that the product is being prescribed or used by health care providers for such use.[14] One example that would not, standing alone, be considered evidence of a new intended use might include the following scenario:

• A pharmaceutical firm tracks sales and distribution metrics. The firm notes that one of its products, approved for use only in adults, is being ordered by and distributed to many medical practices that treat exclusively pediatric populations. The firm does not give any direction to its sales or marketing staff to disseminate samples or information about this product to these pediatric practices.

Similarly, knowledge in combination with conduct that falls within an acknowledged FDA ''safe harbor'' would not be determinative of intended use. For example:

• A pharmaceutical firm tracks sales and distribution metrics. The firm notes that one of its products, approved for the treatment of adult patients with acute lymphoblastic leukemia (ALL), is being ordered by and distributed to many medical practices that treat exclusively pediatric oncology populations. The firm also notes that the National Comprehensive Cancer Network clinical practice guidelines (CPG) for the treatment of ALL in pediatric patients recommends the firm's drug product as a treatment option. The pharmaceutical firm distributes copies of the CPG at medical conferences, following all recommendations made in the revised draft guidance, ''Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices'' (Ref. 8). The firm does not give any direction to its sales or marketing staff to disseminate samples or information about this product to practices that treat pediatric cancer patients exclusively.

We note that in some cases, knowledge that a product was being prescribed or used by health care providers for an unapproved use could be considered relevant to establishing a new intended use where there is additional evidence of intended use (but excluding, as discussed above, evidence that falls within FDA's acknowledged ''safe harbors'' for dissemination of information about an unapproved use of an approved product).

2. Additional Examples That, Standing Alone, Are Not Determinative of Intended Use

There are examples of other circumstances that, standing alone, would not be determinative of intended use. For example, there may be limited instances where a firm disseminates safety information about an unapproved use to health care providers to minimize risk to patients. Such dissemination, on its own, would not ordinarily be dispositive evidence of a new intended use. The scenario below provides one example of a situation in which a firm could disseminate safety and warning information without triggering the prohibitions on distributing a product for an unapproved use and misbranding a product by failing to provide adequate directions for use. The following example is fact-specific and is provided for illustrative purposes only.

• The unapproved use of a firm's approved drug is broadly accepted by the medical community and the firm

[13] The acronym ''API'' in this category includes active drug ingredients, whether or not they are in an approved drug. As used here, ''API'' does not include a biologically active dietary ingredient in a dietary supplement.

[14] Nothing in this rulemaking is intended to change a firm's existing obligations and responsibilities under the FD&C Act, the PHS Act, or FDA's implementing regulations to take action with respect to safety information including: (1) Updating its labeling to ensure that the labeling is not false or misleading or for other reasons; (2) reporting serious adverse events or other postmarketing safety reports to the Agency; or (3) issuing recalls, corrections, and removals. See, for example, 21 CFR 201.56(a)(2) (''[approved human prescription drug and biological product] labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading''); 21 CFR 314.70, 514.8(c), 601.12, 814.39, and 814.108 (concerning supplements and other changes to approved medical product applications, including labeling); 21 U.S.C. 321(n) and 21 CFR 1.21(a) (providing that material omissions can be misleading); 21 CFR 314.80 (postmarketing reporting of adverse drug experiences); 21 CFR 514.80 (records and reports concerning experience with approved new animal drugs); 21 CFR part 803 (obligations under medical device reporting); 21 CFR part 806 (medical device reports of corrections and removals); 21 CFR part 810 (medical device recalls); 21 CFR part 7, subpart B (recalls).

has submitted an efficacy supplement to add the unapproved use to the labeling of the drug. The boxed warning and risk evaluation and mitigation strategy (REMS) materials for the drug warn of potential risks related to the unapproved use in general terms, but the firm disseminates additional specific safety and warning information to health care providers to minimize the risk to patients receiving the drug for the unapproved use. The safety and warning information does not expressly or implicitly promote the efficacy of the unapproved use.

Below are some additional examples that, without other evidence, would not establish a new intended use. This list is not intended to be comprehensive or restrictive. Each scenario is fact-specific, and, under other circumstances or in other contexts, similar material may be evaluated differently.

- A firm's official social media account ''follows'' the social media account for a 501(c)(3) non-profit that supports patients with a rare disease for which there is no FDA-approved treatment. The firm is in the process of investigating one of its FDA-approved products for use in the rare disease that the non-profit account supports. The non-profit account disseminates messages about charity events, scientific conferences, support groups, and rare disease research and drug development. The firm account does not make any comments or otherwise endorse any specific posts on the non-profit account.
- During an internal meeting, a firm's CEO displays a slide of internal sales projections for its approved product. The slide reflects potential sales for an unapproved use that is widely recognized as the standard of care.
- A firm makes corporate filings or submissions to the U.S. Securities and Exchange Commission that include required disclosures of development activities or potential or actual sales for an unapproved use.
- Following a clinical trial, the sponsoring firm prepares a plain-language summary of the aggregated clinical trial results and provides the summary solely to clinical trial participants to acknowledge their contributions to scientific and medical advancement (not to inform prescribing and use decisions). The summary provides a factual, balanced, and complete presentation of the trial results, including relevant safety information and any limitations of the study. The summary does not make any conclusions about the safety or effectiveness of the unapproved product or the unapproved use, and it includes a conspicuous and prominent statement that the product or use has not been approved, cleared, or licensed by FDA.

VI. Proposed Effective Dates

The Agency proposes that any final rule based on this proposed rule will become effective 30 days after the date of publication of the final rule in the **Federal Register**.

VII. Preliminary Economic Analysis of Impacts

A. Introduction and Summary

1. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 13771 requires that the costs associated with significant new regulations ''shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations.'' This proposed rule is not expected to be subject to the requirements of Executive Order 13771 because this proposed rule is expected to result in no more than *de minimis* costs. This proposed rule is a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. We cannot predict how many companies may revise labeling, advertising, or other materials, or otherwise modify their behavior, following issuance of this rule. However, because this rule would merely clarify, but not change, the types of evidence relevant to determining manufacturers' intended use of products, any such changes would be voluntarily undertaken by firms. Because the proposed rule would not extend FDA's authority to additional products or impose any additional requirements on currently regulated products, we expect the proposed rule will impose negligible costs, if any. As a result, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $154 million, using the most current (2018) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

2. Summary of Costs and Benefits

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

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

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

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

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (percent)	Period covered	
Benefits:							
Annualized					7		

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

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (percent)	Period covered	
Monetized $millions/year					3		
Annualized					7		
Quantified					3		
Qualitative	Clarification of intended use interpretation and application						
Costs:							
Annualized					7		
Monetized $millions/year					3		
Annualized					7		
Quantified					3		
Qualitative	Negligible costs, if any						
Transfers:							
Federal					7		
Annualized Monetized $millions/year					3		
From/To	From:			To:			
Other					7		
Annualized Monetized $millions/year					3		
From/To	From:			To:			

Effects:
State, Local or Tribal Government: None
Small Business: None
Wages: None
Growth: None

B. Preliminary Economic Analysis of Impacts

1. Background

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

One important clarification involves a manufacturer's knowledge of unapproved uses of its approved product. Current versions of §§ 201.128 and 801.4 specify that a manufacturer of a drug (§ 201.128) or device (§ 801.4) must include adequate labeling if it knows its product is used for an unapproved purpose. The September 2015 proposed rule (80 FR 57756 at 57764) removed the sentence regarding the requirement to provide adequate labeling if a firm knows its product is being used for an unapproved use. The amended January 2017 final rule (82 FR 2193 at 2217) was intended to clarify FDA's position by requiring manufacturers to include adequate labeling ''if the totality of the evidence establishes that a manufacturer objectively intends that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than ones for which it is approved (if any).''

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

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

2. Benefits of the Proposed Rule

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

products due merely to knowledge of unapproved uses of these products by third parties. We believe this clarification is the benefit of the proposed rule; we request comment on this assumption.

3. Costs of the Proposed Rule

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

C. Initial Small Entity Analysis

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

TABLE 2—SMALL BUSINESS ADMINISTRATION SIZE STANDARDS FOR AFFECTED INDUSTRIES

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

VIII. Analysis of Environmental Impact

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

IX. Paperwork Reduction Act of 1995

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

XI. Consultation and Coordination With Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

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. Plaintiff's Memorandum of Law at 38–40, *Allergan Inc.* v. *United States,* 1:09–cv–01879–JDB (D.D.C. January 15, 2010).
2. Complaint at ¶¶ 35–37, *Par Pharmaceutical Inc.* v. *United States,* 1:11–cv–01820 (D.D.C. October 10, 2011).
3. Citizen Petition from the Medical Information Working Group at 18, FDA–2013–P–1079 (Sept. 3, 2013).
4. Memorandum for the Heads of Executive Departments and Agencies, from Reince Priebus, Assistant to the President and Chief of Staff, ''Regulatory Freeze Pending Review,'' January 20, 2017 (available at *https://www.whitehouse.gov/presidential-actions/memorandum-heads-executive-departments-agencies/*), accessed February 5, 2020.
5. FDA, Guidance for Industry, ''Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers,'' June 2018 (available at *https://www.fda.gov/media/102575/download*), accessed February 5, 2020.
6. FDA, Guidance for Industry and Review Staff, ''Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities—Questions and Answers,'' June 2018 (available at *https://www.fda.gov/media/102683/download*), accessed February 5, 2020.
7. FDA, Guidance for Industry, ''Industry-Supported Scientific and Educational Activities,'' December 1997 (available at

https://www.fda.gov/media/70844/download), accessed February 5, 2020.
8. FDA, Draft Guidance for Industry, ''Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices,'' February 2014 (available at *https://www.fda.gov/media/88031/download*), accessed February 5, 2020.
9. FDA, Draft Guidance for Industry, ''Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices,'' December 2011 (available at *https://www.fda.gov/media/82660/download*), accessed February 5, 2020.
10. Eguale, T., D.L. Buckeridge, A. Verma, et al., ''Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population,'' *Journal of American Medical Association Internal Medicine,* 176(1):55–63, 2016.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 801

Labeling, Medical devices, Reporting and recordkeeping requirements.

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

PART 201—LABELING

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

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

■ 2. Revise § 201.128 to read as follows:

§ 201.128 Meaning of intended uses.

The words *intended uses* or words of similar import in §§ 201.5, 201.115, 201.117, 201.119, 201.120, 201.122, and 1100.5 of this chapter refer to the objective intent of the persons legally responsible for the labeling of an article (or their representatives). The intent may be shown by such persons' expressions, the design or composition of the article, or by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. Objective intent may be shown, for example, by circumstances in which the article is, with the knowledge of such persons or their representatives, offered or used for a purpose for which it is neither labeled nor advertised; provided, however, that a firm would not be regarded as intending an unapproved new use for an approved drug based solely on that firm's knowledge that such drug was being prescribed or used by health care providers for such use. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he or she received the article, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses.

PART 801—LABELING

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

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

■ 4. Revise § 801.4 to read as follows:

§ 801.4 Meaning of intended uses.

The words *intended uses* or words of similar import in §§ 801.5, 801.119, 801.122, and 1100.5 of this chapter refer to the objective intent of the persons legally responsible for the labeling of an article (or their representatives). The intent may be shown by such persons' expressions, the design or composition of the article, or by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. Objective intent may be shown, for example, by circumstances in which the article is, with the knowledge of such persons or their representatives, offered or used for a purpose for which it is neither labeled nor advertised; provided, however, that a firm would not be regarded as intending an unapproved new use for an approved or cleared device based solely on that firm's knowledge that such device was being prescribed or used by health care providers for such use. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he or she received the article, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses.

Dated: September 8, 2020.

Stephen M. Hahn,

Commissioner of Food and Drugs.

[FR Doc. 2020–20437 Filed 9–22–20; 8:45 am]

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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[EPA–R09–OAR–2020–0418; FRL–10013–74–Region 9]

Air Quality Implementation Plan; California; Northern Sierra Air Quality Management District; Stationary Source Permits

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: The Environmental Protection Agency (EPA) is proposing to approve a revision to the Northern Sierra Air Quality Management District (NSAQMD or ''District'') portion of the California State Implementation Plan (SIP). In this action, we are proposing to approve a rule submitted by the NSAQMD that governs the issuance of permits for stationary sources, which focuses on the preconstruction review and permitting of major sources and major modifications under part D of title I of the Clean Air Act (CAA or ''the Act''). We are taking comments on this proposal and a final action will follow.

DATES: Written comments must be received on or before October 23, 2020.

ADDRESSES: Submit your comments, identified by Docket ID No. EPA–R09–OAR–2020–0418 at *https://www.regulations.gov,* or via email to *R9AirPermits@epa.gov.* For comments submitted at *Regulations.gov*, follow the online instructions for submitting comments. Once submitted, comments cannot be removed or edited from *Regulations.gov*. For either manner of submission, the EPA may publish any comment received to its public docket. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information the disclosure of which is restricted by statute. Multimedia submissions (audio, video, etc.) must be accompanied by a written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. The EPA will generally not consider comments or comment contents located outside of the primary submission (*i.e.,* on the web, cloud, or other file sharing system). For