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Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2015-N-2002; Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses"; Further Delayed Effective Date; Request for Comments

Dear Sir or Madam:

The Advanced Medical Technology Association (hereinafter referred to as "AdvaMed") provides these comments in response to the Food and Drug Administration ("FDA" or the "Agency") request for comments on amendments to regulations regarding "intended uses" published in the Federal Register on March 20, 2017, 82 FR 14319 (the "Request for Comments").

AdvaMed is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems. AdvaMed member companies produce technologies that are transforming healthcare through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed's members produce nearly 90 percent of the healthcare technology purchased annually in the United States and more than 50 percent of such technology purchased annually around the world. AdvaMed members range from the largest to the smallest medical technology innovators and companies.

The "intended use" of a medical product is a foundational concept in the application of the Food, Drug, and Cosmetic Act ("FDCA" or the "Act"). It not only controls how a medical product is regulated and the premarket pathway that applies to a medical product, but also dictates the uses for which the product's manufacturer is required to provide adequate labeling, *see* 21 CFR § 801.4. For this reason, it is crucial that FDA's definition of "intended uses" provide manufacturers with clear guidance and take care not to sweep broadly into permitted and protected exchange of truthful, non-misleading information. Unfortunately, FDA's January 9, 2017 final rule on the definition of "intended uses," 82 FR 2193 (the "Final Rule"), does neither.

As discussed further below, as written, the Final Rule will create substantial confusion for medical product manufacturers and could thereby chill crucial interactions between manufacturers other key stakeholders, including patients, healthcare professionals, and payors. FDA's Final Rule is inconsistent with both the Agency's recognition that these types of truthful and non-misleading communications serve to promote the public health and the First

Amendment protection that extends to such communications. To avoid the problems that would be created by the amended "intended uses" definition included in the Final Rule, FDA should abandon the Final Rule and instead return to its original and unambiguous proposal to remove the reference to "knowledge" as set forth in FDA's September 25, 2015 proposed rule regarding the definition of "intended uses," 80 FR 57,756 (the "Proposed Rule").

The Final Rule Is Overbroad, Vague and Creates Confusion Regarding Manufacturer Communications That Are Critical to the Public Health

Given the significance of the definition of "intended uses," it is critical the term's meaning be clear and unequivocal and promote meaningful understanding to manufacturers of the standards to which they will be held. It is equally important that FDA's interpretation of the term "intended uses" not encroach on protected scientific exchange or unnecessarily impede truthful, non-misleading commercial speech. The Final Rule's definition of "intended uses" – which for the first time encompasses a "totality of the evidence" standard – is both overly broad and vague. Far from providing clarity, the Final Rule creates confusion as to what FDA might consider as evidence of an "intended use," including how the Agency will consider communications, such as scientific exchange, that are currently recognized as appropriate and permissible. Moreover, because the "totality of the evidence" standard is more outcome determinative than prescriptive, manufacturers seeking to avoid potential enforcement action will have no choice but to curb important product-related communications.

As described in AdvaMed's comments to the FDA docket regarding *Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products*, there are a broad range of communications and activities in which medical device manufacturers should be able to participate to further public health. These interactions are necessary to ensure access to medical products and informed, safe use of those products.[1]

More specifically, access to and use of medical devices often requires substantial interaction and discussion between medical device manufacturers and healthcare stakeholders, including healthcare professionals. Notably, device manufacturers' ability to communicate with healthcare professionals is important as the safe and effective use of devices many times depends on the user's ability to operate and manage the device. Communications arise in a variety of manners and may relate to both approved and unapproved uses of medical devices. For example, manufacturers often:

- provide training and technical support on medical devices to facilitate safe and effective use of a device;

- provide presentations at educational and medical meetings regarding clinical trial results or research and development data relating to an investigational use;

[1] In response to the second question posed in the Request for Comments, AdvaMed encourages FDA to consider these public health consequences in evaluating its amendments to the definition of "intended uses." AdvaMed also refers FDA to AdvaMed's comments to the FDA docket regarding *Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products*, which contain further discussion of public health consequences of chilling manufacturer communications.

- engage in discussions with healthcare professionals to obtain advice or feedback relating to investigational research and development, including in connection with consultant advisory boards;

- provide information regarding real-world device use and clinical data at the request of healthcare professionals considering treatments for their patients; and

- engage with healthcare professionals in the iterative process of developing and improving medical devices.

Such types of communications are critical to fostering the health of patients undergoing treatment, as well as the general public through development of and access to new medical technologies. Furthermore, manufacturers are often the source of the most up-to-date information about their products. Ensuring robust scientific discourse among healthcare professionals and manufacturers is not only important, but it is also in the best interest of patient care. As FDA itself has recognized, the public health may benefit when healthcare professionals receive truthful and non-misleading scientific and medical information on unapproved uses.

We also note the review cycle for reimbursement and utilization decisions frequently requires manufacturer communications with payors, technology assessment committees, and similar entities about products, for example, during the period after a premarket submission has been made but before approval or clearance is received. These communications are necessary to allow such healthcare decision makers to conduct needed in-depth scientific and economic analyses to determine the products and procedures they will cover. Further, they help provide the complete and accurate scientific data payors require for their independent, internal deliberations.

Increased ambiguity regarding whether these types of communications will be considered evidence of an "intended use" will chill manufacturers' willingness to engage in these activities. Chilling manufacturer communications, in turn, will have a direct impact on the public health, by hindering access to medical technologies, creating barriers to timely quality and efficient healthcare, and impeding legitimate and protected scientific exchange.

Rule is Inconsistent with Efforts to Provide Clarity and Raises Constitutional Concerns for Truthful, Non-Misleading Manufacturer Communications

As detailed in AdvaMed's comments to the FDA docket regarding *Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products*, FDA has long recognized that the public health may benefit when healthcare professionals receive truthful and non-misleading scientific and medical information from manufacturers, including with regard to unapproved uses. *See, e.g., FDA Draft Guidance for Industry – Responding to Unsolicited Requests for Off-Label Information about Prescription Drugs and Medical Devices* (December 2011). In fact, this Final Rule is a departure and does not fit with FDA progress and efforts to-date to review and appropriately clarify its policies regarding manufacturer communications, including principles in its recent January 2017 draft Agency guidance document entitled "Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities—Questions and Answers" among others.

Equally important, the First Amendment imposes significant limitations on the ability to regulate truthful, non-misleading manufacturer speech. This protection is strongest in the context of scientific speech. Such speech has been recognized as "resid[ing] at the core of the First Amendment" and "merit[ing] the highest degree of constitutional protection." *Washington Legal Foundation vs. Friedman*, 13 F. Supp. 2d 51, 62 (D.D.C. 1998)

Even where manufacturer communications involve promotional commercial speech, that speech is still entitled to First Amendment protection. In particular, under the Supreme Court's ruling in *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of New York*, 447 U.S. 557, 566 (1979), commercial speech cannot be restricted unless the restriction is (1) justified by a substantial government interest, and (2) the means used to directly advance the government interest is not more extensive than necessary to serve the interest. *See Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of New York*, 447 U.S. 557, 566 (1979). Moreover, while this baseline level of First Amendment protection applies to all commercial speech, the Supreme Court specifically has recognized that the First Amendment is particularly important "in the fields of medicine and public health, where information can save lives." *See also Sorrell v. IMS Health*, 564 U.S. 552, 566 (2011).

FDA's Amended "Intended Uses" Definition Sweeps Excessively and Unnecessarily

Hudson requires that restrictions on speech be "not more extensive than is necessary," 447 U.S. at 566. In contrast, the Final Rule's "totality of the evidence" standard sweeps broadly, creating significant questions as to whether truthful and non-misleading, scientifically grounded communications might be viewed as potential evidence of an unapproved "intended use." Most strikingly, it is not clear whether the amended standard would encompass specific types of truthful, non-misleading communications that the Agency has recently recognized as valuable.

In particular, although FDA has issued draft or final guidance documents providing clarity on the permissibility of certain manufacturer communications (including responses to unsolicited requests, distributing scientific and medical publications on unapproved new uses, payor communications, and communications "consistent with" FDA-required labeling), the amended rule creates substantial confusion as to whether such permissible communications nevertheless could be considered by FDA as evidence in finding a new intended use. The "totality of the evidence" standard thus undercuts the limited certainty that FDA has been working to provide industry in recent years.

Similarly, while *Central Hudson* requires that a restriction on commercial speech "directly advance [ ] the governmental interest asserted," *id.*, the Request for Comments itself makes clear that the "totality of the evidence" standard is far broader than necessary to serve FDA's articulated interest. In particular, FDA asserts that it is interested in ensuring that it can hold accountable "firms that attempt to evade FDA's medical product regulation by making no claims, or at least no explicit claims, about their products." 82 FR at 14,321-22. While AdvaMed recognizes FDA's interest in this regard, the examples cited in FDA's Request for Comments almost exclusively relate to activities and communications ~~i~~involving the distribution or promotion of illicit drugs. The examples in the Request for Comment also involve either clearly false or misleading speech (such as labeling that describes products containing the active ingredients in prescription drugs as "natural" or "herbal" supplements) or conduct that would

violate criminal statutes other than the Food, Drug, and Cosmetic Act (such as the Controlled Substances Act or the mail or wire fraud statues). The "totality of the evidence" standard is not necessary to target speech or conduct that is subject to enforcement through currently available means.

If FDA's interest is in ensuring that manufacturers and distributors of illicit drugs do not evade regulation via misleading statements regarding "intended use," the "intended uses" definition should be tailored to "directly advance" that interest. The current Final Rule, however, is not so narrowly tailored; to the contrary, the "totality of the evidence" standard potentially encompasses a wide variety of lawful and legitimate activities. Moreover, given the myriad ways in which the definition of "intended uses" arises in FDA regulation and enforcement, incorporating a vague "totality of the evidence" standard within the "intended uses" definition expands the standard's impact far beyond circumstances involving the manufacture or distribution of illicit drugs. Because the "totality of the evidence" standard does not "directly advance" the interest asserted by FDA, the Final Rule's "intended uses" definition fails to comport with the First Amendment.[2]

Mere Knowledge Should Not Be Considered Evidence of an Intended Use

FDA's Final Rule also creates substantial uncertainty as to the consideration that FDA will give to a manufacturer's knowledge of third-party use of its products in considering the manufacturer's "intended uses." The Proposed Rule correctly assured that manufacturers would not be placed in the untenable position of facing potential criminal and civil liability based solely on actual or constructive knowledge of unapproved uses of their products in the marketplace. By removing the clarifying language in the Proposed Rule, the Final Rule suggests that FDA may consider a manufacturer's mere knowledge as sufficient evidence of an "intended use." This is inappropriate. A manufacturer's "intended uses" should be determined based upon the manufacturer's affirmative conduct and firmly grounded on claims made by a manufacturer to promote its products, not a firm's knowledge of a third-party use.

As an initial matter, it is inappropriate to hold manufacturers responsible for the use of their products by third parties over whom they have no control. Equally importantly, doing so may have unintended – and undesirable – effects that are detrimental to the public health. Such an approach also does not fit with FDA and stakeholder efforts to move from concept to implementation of a real-world evidence model that encourages collaboration and potential leveraging of data to support new product innovations for U.S. patients (see *FDA Draft Guidance for Industry—Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices* (July 2016). AdvaMed strongly encourages FDA to consider this and other potential detrimental impacts of a standard that leaves open the possibility that mere knowledge might be sufficient to establish an "intended use."

[2] In response to the first question posed in the Request for Comments, AdvaMed notes that the situations outlined in the Request for Comments do not justify an overly broad standard for determining "intended uses," as the identified situations are addressable through other means that are far less restrictive and more narrowly tailored to FDA's articulated concern.

FDA Should Abandon the Final Rule and Adopt a Clear and Appropriate Definition of "Intended Uses"

For all of these reasons, AdvaMed strongly urges FDA to abandon the vague and overly broad "totality of the evidence" standard articulated in the Final Rule and revert to the approach set forth in the Proposed Rule. At a minimum, if FDA does not revert to that approach, FDA should adopt a standard for determining "intended uses" that makes clear that (1) legitimate, protected scientific exchange, (2) truthful, non-misleading communications (including commercial speech), and (3) mere knowledge of unapproved use by third parties do not constitute evidence of an "intended use."[3] In addition, to ensure robust and full exchange of scientific discourse in the benefit of the public health, AdvaMed encourages FDA to issue a policy or framework addressing manufacturer communications regarding unapproved uses of approved or cleared medical products that will safeguard appropriate manufacturer communications. As part of this policy or framework, AdvaMed urges FDA to provide much-needed clarification regarding the types of manufacturer communications and activities that constitute protected "scientific exchange."

As noted in AdvaMed's comments to the FDA docket regarding *Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products*, the healthcare environment is rapidly evolving. The need for stakeholder access to truthful and non-misleading product information has never been greater. Clear Agency policy can and should play a critical role in supporting scientific progress and overall advances in high quality medical device technologies and optimal care for U.S. patients.

Sincerely,

/s/

Khatereh Calleja, JD
Senior Vice President
Technology and Regulatory Affairs

[3] In response to the fourth question posed in the Request for Comment, AdvaMed notes that it does not perceive a distinction between the "totality of the evidence" standard included in the Final Rule and an "any relevant source of evidence" standard. Rather than adopting this type of vague and sweeping standard, which is likely to chill important communications between manufacturers and other stakeholders, FDA should adopt a standard that clearly carves out legitimate and accepted scientific exchange and other truthful, non-misleading communications.