April 19, 2017

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

Re: Docket No. FDA-2016-N-1149; Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Public Hearing; Request for Comments

Dear Sir or Madam:

The Advanced Medical Technology Association (hereinafter referred to as “AdvaMed”) is pleased to provide these comments in response to the Food and Drug Administration (“FDA” or “Agency”) request for information and comments on specific questions and background information published in the Federal Register on September 1, 2016 regarding “Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products” (hereinafter referred to as the “FR notice”) 81 FR 60299. We also thank FDA for the opportunity to provide a statement at its public hearing held on this topic on November 9-10, 2016.

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.

AdvaMed welcomes FDA’s efforts to review and clarify its policies regarding manufacturer communications on unapproved uses of approved and cleared medical products and to consider stakeholder views as part of its efforts. AdvaMed notes that FDA recently issued a January 2017 memorandum describing the Agency’s views on the public health interests and First Amendment considerations related to this topic entitled “Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products” (or “Agency Memorandum”). Notably, AdvaMed supports many of the principles contained in the two draft Agency guidance documents also released in January 2017 entitled “Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers” (or “Consistent Communications Draft Guidance”) and “Drug and Device Manufacturer Communications with Payors, Formulary..."
Committees, and Similar Entities—Questions and Answers” (or “Payor Communications Draft Guidance”). AdvaMed plans to submit comments on these draft guidance documents to the respective dockets.

Our general comments are provided below and are followed by specific comments related to questions posed in the September 2016 FR notice. Our comments are intended to provide industry feedback regarding the need for clear and articulated protection of appropriate communications concerning unapproved uses of approved or cleared medical devices. AdvaMed stands ready to assist FDA in its review and development of policy regarding such communications with the ultimate goal of ensuring appropriate discourse in support of the public health.

GENERAL COMMENTS

FDA has long recognized that truthful, non-misleading speech regarding unapproved uses of approved or cleared medical products can serve important public health goals. As early as 1982, the Agency acknowledged that manufacturers’ responses to unsolicited requests regarding their products, including those relating to unapproved uses, are part of the “exchange of valid and legitimate information…” about the product and are not regulated as “labeling” under FDA authorities. FDA Position on the Concept of Solicited and Unsolicited Requests (April 22, 1982).

More specifically, FDA has recognized that the public health may benefit when healthcare professionals receive truthful and non-misleading scientific and medical information on unapproved uses. See Agency Memorandum; See also FDA Revised Draft Guidance for Industry—Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices (February 2014) (or “Distributing Scientific and Medical Publications Revised Draft Guidance”) and FDA Draft Guidance for Industry—Responding to Unsolicited Requests for Off-Label Information about Prescription Drugs and Medical Devices (December 2011) (reiterating the same position).

AdvaMed agrees that truthful, non-misleading discourse regarding unapproved uses of approved or cleared medical products is in the best interest of the public health. The need for such discourse is particularly compelling because the practice of medicine permits physicians to use FDA-approved or cleared products for unapproved purposes, within the exercise of their medical judgment. As the Supreme Court has recognized in the context of medical devices in particular, “off-label’ usage of medical devices (use of a device for some other purpose than that for which it has been approved by the FDA) is an accepted and necessary corollary of the FDA’s mission to regulate . . . without directly interfering with the practice of medicine.” Buckman Co. v. Plaintiffs’ Legal Committee, 531 U.S. 341, 350 (2001). For this reason, the Federal Food, Drug & Cosmetic Act (“FDCA” or the “Act”) specifically provides that nothing in the Act “shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate healthcare practitioner-patient relationship.” 21 U.S.C. § 396. Indeed, FDA itself has
recognized that “off-label uses of medical products have made valuable contributions to patient care.” FDA, Response Letter to Citizen Petition of the Medical Information Working Group, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079 (June 6, 2014).

Physicians make significant efforts to keep abreast of the latest medical and scientific information on medical products to help provide care for their patients, but keeping up with hundreds of journals, publications, seminars, and the deluge of online information can often be difficult. Notably, manufacturers are often the source of the most up-to-date information about their products. As has been recognized on both public policy and constitutional grounds, ensuring scientific discourse is not only important, but it is also in the best interest of patient care and the overall public health.

The importance of truthful, non-misleading commercial speech – and its protection under the First Amendment – has been confirmed by recent case developments. The Supreme Court has long recognized that such speech cannot be restricted unless the restriction is justified by a substantial government interest, and 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). The Supreme Court also has confirmed that “speech in aid of [medical product] marketing … is a form of expression protected by the Free Speech Clause of the First Amendment.” Sorrell v. IMS Health 564 U.S. 552, 557 (2011).

AdvaMed recognizes the substantial government interests in protecting the public health and ensuring communications regarding medical products are truthful and non-misleading. We firmly believe that truthful, non-misleading communications regarding unapproved uses of approved or cleared medical products can substantially advance these interests. Particularly with respect to medical devices, such communications support clinical decision making and the delivery of timely, quality and efficient healthcare as well as facilitate research to support new advances in healthcare. An FDA policy that permits such communications would not undermine the Agency’s interest in the development of robust scientific data on safety and effectiveness, particularly in light of payor and value-driven healthcare requirements. Such a policy would also not undermine the Agency’s interest in protecting the integrity and reliability of information regarding medical products. A variety of safeguards exists to disincentivize and enforce against false and misleading speech, and AdvaMed believes that appropriate disclosures can serve an important role in ensuring that communications based on valid scientific evidence do not present a misleading impression.

As confirmed by recent case developments, a policy that prohibits truthful and non-misleading communications regarding unapproved uses of approved or cleared medical products is not narrowly drawn to directly further FDA interests and is more extensive than necessary. Relying on the principles set forth in Central Hudson and Sorrell, in 2012, the U.S. Court of Appeals for the Second Circuit 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-approved drug.” United States v. Caronia, 703 F.3d 149, 169 (2d Cir. 2012). The court concluded that while the government’s interests in drug safety and the public
health were substantial, its construction of the FDCA to prohibit off-label promotion did not directly advance those interests. *Id.* at 166-67. Likewise, because physicians can prescribe and patients can receive drugs off-label, even if pharmaceutical manufacturers could not promote drugs for such uses, prohibition of truthful promotion did not directly further the government’s goals as “the government’s prohibition of off-label promotion by pharmaceutical manufacturers provides only ineffective or remote support for the government’s purpose.” *Id.* at 167 (citations omitted). The court also concluded that a ban on off-label promotion was not narrowly drawn to protect its interests, citing several less restrictive methods the government could have used to protect its interests instead, such as developing a warning or disclaimer system. *Id.* at 167-68.

In *Amarin Pharma, Inc. v. U.S. Food and Drug Administration*, the U.S. District Court for the Southern District of New York ruled that “[w]here the speech at issue consists of truthful and non-misleading speech promoting the off-label use of an FDA-approved drug, such speech, under *Caronia*, cannot be the act upon which an action for misbranding is based.” 119 F.Supp.3d 196, 227 (S.D.N.Y. 2015). Most recently, in a criminal enforcement proceeding, the Department of Justice acknowledged this principle by agreeing to proposed jury instructions stating that it is “not a crime for a device company or its representatives to give doctors wholly truthful and non-misleading information about the unapproved use of a device.” Proposed Jury Instructions, *U.S.A. v. Vascular Solutions, Inc. & Howard C. Root*, Crim. No. SA:14-CR-926-RCL, (Jan 7, 2016).

The First Amendment requires FDA to adopt a less speech-restrictive alternative to a prohibition on off-label communications where that alternative furthers the Agency’s interest in protecting the public health. Allowing truthful and non-misleading communications regarding unapproved uses with appropriate disclosures is such an alternative approach. AdvaMed recognizes that in the Agency Memorandum FDA determined that an approach of allowing proactive communications regarding unapproved uses would not advance the Agency’s interests. Agency Memorandum at 30. AdvaMed disagrees with this conclusion. In particular, AdvaMed disagrees with the Agency’s concern that this approach would result in the wide dissemination of information “based on conjecture or extrapolation from limited data.” Agency Memorandum at 30. As discussed in detail below, manufacturers would continue to develop robust data to demonstrate the safety and effectiveness of medical products. And FDA maintains the ability to ensure the integrity and reliability of such communications, preventing harm or deception, through the application of appropriate evidentiary standards and appropriate disclosures. AdvaMed also firmly believes that permitting truthful and non-misleading communications regarding unapproved uses with appropriate disclosures supports clinical decision making and the delivery of timely, quality and efficient healthcare and facilitates research to support new advances in healthcare.

Courts have recognized that the use of disclosures to guard against misleading impressions is an appropriate alternative approach to prohibiting speech under the First Amendment. For example, in *Pearson v. Shalala*, the United States Court of Appeals for the District of Columbia Circuit cited Supreme Court cases “pointing to disclaimers as constitutionally preferable to outright suppression” in endorsing the use of disclaimers to avoid misleading dietary supplement claims. 164 F.3d 650, 657 (D.C. Cir. 1999) (citing *Peel v. Attorney Registration and Disciplinary Board of West Virginia*)
Comm’n of Illinois, 496 U.S. 91, 110 (1990); In re R.M.J., 455 U.S. 191, 206 n.20 (1982); and Shapero v. Kentucky Bar Assn., 486 U.S. 466, 478 (1988)). More recently, in considering whether particular statements that a pharmaceutical manufacturer proposed to make regarding an unapproved use of its product, the Southern District of New York endorsed the use of disclosures to ensure that the manufacturer’s statements did not give a misleading impression. See generally Amarin, 119 F.Supp.3d 196. The disclosures reviewed by the court – and assented to by FDA in that context – included that the unapproved use at issue had not been approved by FDA and that the drug’s impact on certain health conditions had not been determined and was being studied. Id. at 230-31.

The First Amendment does not protect false or misleading commercial speech and robust FDA authorities exist that disincentivize and guard against such speech. In particular, FDA has the authority to address false and misleading speech through administrative warning letters and civil monetary penalties, civil false claims act cases, and in appropriate cases, criminal misbranding charges. This federal authority is overlaid by state laws – such as false advertising and unfair trade practices – that also may be used to address false or misleading statements regarding approved or cleared medical products.

AdvaMed believes that it is both possible and imperative to develop a balanced and rational policy clearly addressing manufacturer communications regarding unapproved uses of approved or cleared medical products that both respects these First Amendment principles and furthers the public health. AdvaMed also considers it critical that any such policy be sufficiently tailored to account for factors pertaining to such communications that are relevant to, and in some instances unique to, medical devices. As discussed further in our specific comments that follow, there are a broad range of communications and activities in which medical device manufacturers should be able to participate in order to further public health (e.g., payor communications, manufacturer-implemented product training, and technical support). Any standards developed to ensure that manufacturer communications are truthful and non-misleading should be sufficiently flexible to account for these different types of communications and activities to avoid significantly chilling the continued development and evaluation of medical devices and the communication of key safety information regarding medical devices. AdvaMed believes that such an outcome would not advance FDA’s regulatory purpose of protecting the public health. We also provide considerations regarding appropriate evidentiary support and disclosures for certain types of communications as well as advocate for providing an explicit safe harbor for value-based communications among medical device manufacturers, hospital committees, healthcare practitioners, payors, and other stakeholders.

SPECIFIC COMMENTS

It is important for FDA to take a multi-factorial approach in the framework it develops for medical device manufacturers’ communications about unapproved uses of approved/cleared medical products to account for the broad range of activities conducted by a manufacturer in furtherance of public health and patient safety. Such truthful, non-misleading communications can play an important role, including improving clinical decision making and facilitating research to support new advances in healthcare. [Questions 1, 7].
As FDA has recognized in various contexts, there are substantial differences between medical devices and other medical products. Such distinctions include the wide scope and nature of the products, the average product lifecycle, and the applicable regulatory framework. Unlike other medical products, medical devices are often multifaceted, with various technical features, components, and accessories. The design, use, and understanding of these devices is often complex, and this necessitates educational programs and engagement with the healthcare community throughout the lifecycle of the medical device, in order to support safe use and avoid the chilling of device research and innovation.

Notably, access to and use of medical devices typically requires substantial and timely interaction and discussion between medical device manufacturers and highly trained healthcare professionals. The use of medical devices often entails a medical procedure and, in many cases, surgery. As discussed later in our comments, manufacturers often provide training and technical support on medical devices for physicians to help facilitate a physician’s safe and effective use of the device. The decision to use a particular medical device often is preceded by consultations with multiple healthcare specialists, further testing, and detailed discussions of the surgical and non-surgical options available given the particular health circumstances of an individual patient. Following initial launch of a medical device, manufacturers gain unique insights into the use of their devices in specific patient populations, and often they also collect substantial clinical data that could assist physicians in patient care decisions. In many cases, off-label clinical data may be substantial and scientifically robust even if not alone sufficient to meet FDA standards for inclusion in the product labeling.

Finally, medical device technology typically evolves in an iterative progression with continual, incremental improvements over time. Unlike drugs and biologics, the average lifecycle for many medical devices may be as short as 18 months. Thus, timely information is particularly important to educate the healthcare community about new technologies, a number of which provide relief for patients who suffer from conditions that currently have no treatment. Moreover, communications between providers and manufacturers of medical devices is essential to support use of ever-increasing cutting edge and complicated technology (e.g., complex software algorithms, use of advanced materials, etc.). FDA should take care not to discourage or harm the flow of such critical exchange between manufacturers and healthcare professionals using their products. Furthermore, ongoing discourse with the healthcare community about potential new technological advances can support early product development, continued product innovation and improvements, mitigation of risks, and overall advancement of the public health.

As FDA has recognized, “[f]or medical devices, available evidence [supporting device approval or clearance] is traditionally comprised of non-clinical and, in some cases, clinical studies conducted and provided to FDA by the device manufacturer or sponsor.” *FDA Draft Guidance for Industry—Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices* (July 2016) ("Real-World Evidence Draft Guidance") at 5. In addition, however, “a wealth of data covering medical device experience exists and is routinely collected in the course of treatment and management of patients.” *Id.*
Feedback from the healthcare community regarding unmet medical needs is also critical to guiding decisions regarding new device innovation and supporting continued device evolution and enhancement. Communication with healthcare professionals regarding the challenges they encounter and needs they identify in the real world in an ongoing, iterative process can lead to more timely product improvements and improved patient healthcare options. Real-time engagement with healthcare professionals regarding ongoing medical device development may also increase their awareness of clinical trials, and thereby facilitate greater patient participation in medical device research; furthermore this is also required as part of the design input process under 21 CFR Part 820.

Developing innovative technology requires a great deal of time and significant capital investment, which can often disincentivize new medical product innovation in the United States. In particular, this can have the unintended consequence of eliminating device companies, especially small and start-up companies, from the marketplace or discouraging them from entering in the first place. Increased ability to rely on real-world evidence and data generated for other purposes can play an important role in supporting new product development and additional or expanded indications for use. Ultimately, patients benefit as allowing medical device developers to better leverage existing evidence and reducing the cost of clinical trials can lead to more timely introduction of safe and beneficial technologies.

For example, experience in the field following marketing approval or clearance may provide critical safety or effectiveness information. Additional information regarding matters such as device placement and use in combination with other products may become available after a product is on the market. Facilitating responsible, scientifically accurate discussion of this type of information therefore may allow healthcare professionals greater access to important safety and effectiveness information.

In light of these unique aspects of medical device technologies, facilitating communication between medical device manufacturers and healthcare stakeholders, including scientists, researchers, healthcare professionals, and investigators, regarding approved or cleared medical devices may be of particular benefit to the public health. Increased communication regarding unapproved uses may improve clinical decision making and facilitate research to support new advances in healthcare. Real-time engagement with healthcare professionals regarding ongoing medical device development may also increase their awareness of clinical trials, and thereby facilitate greater patient participation in medical device research.

To address the needs for ongoing dialogue with the healthcare community, medical device manufacturers, in particular, engage in many different categories of activities in furtherance of product development, patient safety, and quality and efficient healthcare. Notably, permitting device manufacturers to support the safe and effective use of approved or cleared devices when healthcare professionals have elected to use a device for an unapproved use is important to ensuring the safe and effective use of such devices and is in the interest of the public health. The following examples illustrate the varied types of communications and activities in which device manufacturers engage consistent with the unique aspects of device medical technologies:
• Manufacturer training of healthcare providers on the use of medical devices – which may even be required by FDA – plays an important role in achieving positive outcomes with device therapies. Unlike other medical products, the safe and effective use of medical devices often depends on the user’s ability to operate and manage the device. For users to safely prescribe drugs and biologics, it is important that they understand the labeling, including information regarding dosage, warnings, and contraindications. To safely use medical devices, users also need to understand how to use the device itself, including specific techniques to safely and effectively employ the product and how to effectively troubleshoot when clinically rare situations occur. In this context, providing users with current information on potential risks associated with unapproved use of an approved or cleared device in product training may be critical to mitigating potential patient safety risks. And in many situations, training requested by healthcare professionals concerns uses that are supported by clinical practice guidelines, peer-reviewed reprints, and/or current standards of care. Allowing manufacturers to proactively offer training to healthcare professionals under such circumstances furthers the public health.

• Medical device manufacturers are often requested to provide technical support for their devices, including in the context of patient procedures, in order to help ensure a provider’s safe and effective use of the device. In this context as well, providing current, scientifically sound information and technical assistance to support understanding of the use (and risks) of a device, which may include information regarding unapproved uses, is important to facilitating safe and effective deployment of the device in real-world, real-time scenarios when a healthcare professional chooses to deploy a device for such use. Another example would be in the in vitro diagnostic (IVD) industry, clinical laboratories are permitted and frequently validate off-label uses of IVDs. Information from manufacturers about their assays can facilitate safer and/or more effective modification of such products to support patient care.

In these and other contexts, facilitating the ability of medical device manufacturers to provide truthful and non-misleading information for uses of approved or cleared products and associated risks promotes the safe and effective use of these products by healthcare professionals, and should be encouraged in order to further the common goal of patient safety.

AdvaMed fully recognizes that risks may exist if information communicated to healthcare professionals is not truthful, accurate, or scientifically sound, but we believe that safeguards are in place to guard against this type of communication. First and foremost, as discussed in greater detail below, AdvaMed member companies take seriously their obligations and responsibility to support the public health, and strive to communicate responsibly regarding their products, including: (1) ensuring communications are based on robust data and analyses using scientifically and statistically sound methodologies, (2) ensuring communications clearly disclose appropriate contextual information about the data presented, and (3) ensuring that data are represented accurately, including disclosure of any limitations in the data and analytical methodologies. To this end, medical device manufacturers endeavor to ensure that communications regarding unapproved uses of their approved or cleared products are truthful, non-misleading, and scientifically sound.
It is imperative that any framework developed by FDA on communications related to unapproved uses of approved or cleared products should appropriately account for the broad range of appropriate activities conducted by device manufacturers in furtherance of public health and patient safety. As discussed in the comments that AdvaMed submitted to FDA on March 27, 2012 related to scientific exchange in response to the FDA Federal Register (FR) regarding “Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed” (“2012 AdvaMed Comments on Scientific Exchange” included as Attachment A to this comment for ease of reference), AdvaMed does not believe that FDA should determine whether a type of activity is impermissible based on one specific factor to the exclusion of other factors. Instead, FDA should consider the context and content of the communication, including the type of issues presented; the content and quality of materials presented; the nature of the person or entity presenting and the audience; and objective circumstances surrounding the presentation. As part of the consideration of these factors, it is important to consider the scientific value of the exchange. For example, an activity that is aimed at soliciting medical or scientific feedback or educating listeners on medical or scientific issues is not in of itself promoting or commercializing a product nor is a communication simply promotional by reason that the audience is a payor. Nevertheless while we appreciate FDA substantial efforts to develop helpful draft guidance this year on specific types of permissible manufacturer promotional communications, we urge care as not to impose any policy that bars truthful and non-misleading communications, whether deemed promotional or otherwise, under a framework.

Further, as discussed in more detail below, the framework should provide the level of disclosures and scientific evidentiary support needed to ensure the communications are truthful and non-misleading. For example, communications regarding unapproved uses in promotional materials may need more robust disclosures and a higher level of scientific evidentiary support to ensure that the communications are not misleading.

As discussed in our attached 2012 AdvaMed Comments on Scientific Exchange, scientific and medical communications and activities appropriate for designation as “scientific exchange” include, among other examples, presentations at educational and medical meetings regarding clinical trial results or research and development data for an investigational use, discussions with healthcare professionals to obtain advice or feedback relating to investigational research and development, and discussions with consultants such as during advisory boards. These activities are critical to the continued development, iteration, and evolution of medical devices in support of serving the public health and treating patients with unmet medical needs.

Consistent with our 2012 AdvaMed Comments on Scientific Exchange, AdvaMed also again urges FDA to further clarify the types of activities that constitute scientific exchange. AdvaMed applauds FDA and strongly concurs with the following statement in the Agency Memorandum: “[I]t has long been FDA policy not to consider a firm’s presentation of truthful and non-misleading scientific information about unapproved uses at medical or scientific conferences to be evidence of intended use when the presentation is made in non-promotional settings and not accompanied by promotional materials.” Agency Memorandum at 21. However, AdvaMed is requesting further guidance on the practical application of this policy. Specifically, FDA should
clarify that this policy covers presentations of such data and engagement by academic researchers, clinical investigators, or employees of the respective manufacturer where accompanied by appropriate disclosure. Furthermore, FDA guidance should clearly recognize the appropriateness of such data in communications outside of the medical or scientific conference as such information remains truthful and non-misleading.

**FDA should provide further clarity on what is considered information relating to unapproved uses of approved or cleared medical products, i.e., “off-label” information versus information that does not create a new intended use (or “out-of-label” information) in its development of a framework on manufacturer communications** [Question 5].

AdvaMed believes it is important as an initial step in setting standards for manufacturer communications regarding unapproved uses of approved or cleared medical products to provide a clear definition of the term “off-label” versus information “consistent with labeling” (sometimes referred to as “out-of-label” information). AdvaMed appreciates that the recent FDA draft guidance documents address aspects of communicating information that does not appear in the product label but is consistent with the label or related to an approved indication. For example, the Consistent Communications Draft Guidance describes how FDA evaluates communications that present information not contained in the labeling but that may be “consistent” with the FDA-required labeling. Such medical device manufacturers’ communications may pertain to a use that has been approved or cleared by FDA, but it does not explicitly appear in the approved product labeling (for a device subject to premarket approval) or statement of intended uses (for a device subject to premarket notification). An example of such information would be data developed by a manufacturer relating to outcomes associated with their devices, such as hospital readmission rates for patients treated with an approved or cleared device for an approved use. Such information often does not appear in the labeling, but it is useful to both healthcare professionals and payors, particularly given the shift to an increased focus on value-based healthcare. This type of information does not serve to introduce a new intended use (i.e., it is consistent with, but not contained in, the FDA-required labeling).

AdvaMed believes that the Agency should expand upon the principles in the recent draft guidance documents to permit a wider array of communications that do not introduce a new intended use and provide more clarity on device-specific communications that are consistent with the labeling of the approved or cleared product, including examples for communications related to 510(k) cleared devices with general indications for use. We believe there are additional communications that may be “consistent with” the approved labeling as defined in this draft guidance document (i.e., do not create a new intended use). FDA’s policies should account for these types of communications.

Furthermore, AdvaMed commends FDA undertaking of the Payor Communications Draft Guidance to outline its thinking regarding communications to payors and similar entities as well as provide answers to frequently asked questions, which is helpful in light of the evolving healthcare system and the criticality of these manufacturer communications. We also appreciate FDA efforts to outline policies that are relevant to device manufacturers, such as appropriate entities in the device space (e.g., technology assessment panels) for which healthcare economic
communications are appropriate and for which there are varying types of and examples of accurate and scientifically grounded information appropriate for both approved/cleared and investigational products. We concur with FDA that such information can aid payors and other healthcare decision makers to plan and budget for coverage and/or reimbursement prior to approval and/or clearance. In fact, ensuring such exchange amongst manufacturers and healthcare community is a policy imperative. In that vein, FDA should explicitly reference policies, including relevant principles or concepts, that are applicable to healthcare economic information communications of device manufacturers as well as communications with healthcare providers in the Payor Communications Draft Guidance. AdvaMed also plans to separately submit comments specific to each draft guidance document.

As the information relates to product uses that have already been approved or cleared by FDA, any safety concerns associated with the dissemination of off-label information are further mitigated. AdvaMed acknowledges FDA concerns regarding whether, if permitted to freely engage in communications regarding unapproved uses, manufacturers would have appropriate incentives to conduct research necessary to gain FDA approval or clearance for new uses. These concerns, however, do not apply in the context of communications that do not introduce new intended uses, as FDA has already reviewed the uses at issue. In the example of the hospital readmission data, for instance, the information involves the same condition and patient population for which FDA approved or cleared the medical device, but provides additional information that FDA has not reviewed.

AdvaMed urges FDA to make clear that that the full scope of information that does not appear in the approved labeling but does not introduce a new intended use is appropriate where such information is supported by valid scientific evidence. Such guidance would significantly clarify FDA’s position regarding such communications.

AdvaMed recognizes that there are certain types of communications that would not be appropriate or that could implicate safety concerns that are not appropriate. For example, if FDA has considered data or information in a marketing application but denied that application because the data was not adequate or otherwise deficient, communicating that same data (or the same type or level of data) with respect to the unapproved use in a promotional context would not be appropriate. This would be distinct from a safety notice or other communication for the purpose of scientific exchange.

Changes to the healthcare system necessitate that medical device manufacturers be able to communicate with payors and other stakeholders regarding unapproved uses to support timely, quality and efficient healthcare [Question 1.b, 2]

As FDA’s Federal Register notice recognizes, the healthcare system is rapidly changing. Payors, hospitals, and other healthcare system stakeholders are increasingly focused on assessing the value of healthcare products and services and efforts to help curb the costs of healthcare while improving patient outcomes through the use of clinical goals and efficiency measures. The Department of Health and Human Services (HHS) itself is encouraging these efforts to contain costs and has implemented a number of pilot programs focused on value-based care.
Medical technology manufacturers are uniquely poised to drive value-based healthcare solutions that can support the healthcare industry’s transformation from volume- to value-based healthcare delivery, and its efforts to improve outcomes while reducing costs. Notably, manufacturers have long ago evolved from “widget producers” into complex organizations that understand the need for strategic partnerships with healthcare players to move global healthcare in a direction that is sustainable from a quality and cost perspective for the long term. In that vein, discussions amongst medical device manufacturers, hospital committees, healthcare practitioners, payors and other stakeholders are critical to support value-based healthcare efforts. These efforts demand more communications between stakeholders, including in connection with reviews of services, products, and integrated solutions designed to improve patient and healthcare system outcomes by improving the quality of care or reducing associated expenses. The need for stakeholder access to truthful and non-misleading product information at this time in a rapidly changing healthcare environment, increasing information from third parties available from the internet and other sources, move toward greater patient engagement and understanding of their disease or therapies, and drive for efficient and effective healthcare and a value-based model makes facilitating these critical communications a policy imperative. Providing an explicit safe harbor for such beneficial value-based communications, which should include, for example, case study and big-data analytics, is needed in order to support the public health and serve patients, healthcare providers, and today’s healthcare system.

FDA’s Payor Communications Draft Guidance sets out FDA’s approach to implementing the provisions in the 21st Century Cures Act to explain what healthcare economics information manufacturers may share with payors and similar entities. AdvaMed appreciates that in the Payor Communications Draft Guidance, FDA recognizes that manufacturers may communicate with payors about investigational products. See Payor Communications Draft Guidance at 15-17. Pipeline discussions regarding products still in development or not yet approved for the use under consideration are critical to supporting high quality and value-driven care.

FDA indicated in the Payor Communications Draft Guidance that the audience for the healthcare economic information communications does not include healthcare providers making individual patient prescribing decisions or consumers. While it appears that FDA intended the guidance to be specific to payors and similar entities, we would suggest clarification that the principles outlined in the draft guidance also apply to communications with healthcare professionals. The reasoning is presumably that payors have greater expertise and ability to assess scientific data as well as the time to review them in a deliberate process. However, those same factors support allowing healthcare professionals to receive communications about off-label uses that are scientific in nature and based on generally-accepted scientific standards.

Furthermore, the statutory provision is limited to information “related to” the approved indications of drugs, and so FDA only addressed on-label uses in the Payors Communications Draft Guidance. However, the reasoning supporting the sharing of healthcare economic information “related to” on-label use also supports the ability of manufacturers to share healthcare economic information that may relate to off-label uses.
AdvaMed has identified a number of examples that follow of the types of situations where the ability to share healthcare economic information related to off-label uses would be of value to manufacturers, payors and healthcare providers while not undermining FDA’s public health and safety interests. Furthermore, we believe such policies advance the critical goal of high-quality, efficient, patient-centered care and are, therefore, in the interest of the public health. A clear regulatory regime can advance patient care through transparent and unambiguous protection for these critical communications. The public health necessitates such protection as part of a modern regulatory risk based framework that does not inhibit, but rather encourages improved clinical efficiencies and optimizing of operations.

**Permitting Communications to Payors about New Uses in Anticipation of Approval**

The review cycle for medical device reimbursement and utilization decisions frequently requires communications with payors, technology assessment committees, and similar entities about products during the period after a premarket submission has been made but before approval or clearance is received. The Payor Communications Draft Guidance recognizes communications with payors, formulary committees, or similar entities. However, the review cycle for medical device reimbursement and utilization often requires discussion with other persons within healthcare systems, including value committees as well as technology assessment committees. As previously stated, the communications described in the Payor Communications Draft Guidance should also specifically reference these and other similar entities that undergo review of products as reflected in the guidance and better reflect today’s modern healthcare environment. 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. It should be noted that payor coverage policies are distinct from the FDA premarket approval and clearance process. Interactions with payors regarding potential product coverage do not constitute promotion but, rather, are intended to provide the complete and accurate scientific data payors require for their independent, internal deliberations. These analyses – and the discussions they require with medical device manufacturers – must occur prior to a product approval or clearance in order to ensure timely coverage and reimbursement once approval or clearance is received.

Providing information regarding certain devices prior to clearance or approval is necessary to permit planning by healthcare facilities and promote investment in innovation. For example, large capital equipment devices generally require substantial investment by a healthcare facility, including, in some cases, building additional space or modifying the existing physical space within the healthcare facilities. Capital equipment devices may also be interconnected with other devices or non-device equipment, requiring coordinated planning across multiple types of devices. And, once installed, capital equipment devices may be used by a healthcare facility for a decade or more. Given this substantial investment, healthcare facilities include capital equipment purchases in long-term planning and must plan and budget for such purchases significantly in advance of the actual purchase. To do so, healthcare facilities often request information regarding capital equipment devices in development. Such information may include pricing estimates, device dimensions and installation requirements, performance specifications, potential future product modifications, and interfacing products, as well as demonstrations of
devices in development. We note that some of these considerations are reflected in the recently released Payor Communications Draft Guidance. AdvaMed also submitted additional comments specifically in response to that draft guidance.

A straightforward improvement would be to explicitly permit manufacturers to share information with payors on new FDA submissions and pending approvals or clearances of new uses (currently off-label but which are the subject of the submission) in advance of approval or clearance. FDA has already explicitly permitted such communications with regard to unapproved products in the Payor Communications Draft Guidance. As FDA noted, this information sharing facilitates the acceptance and availability of new devices once they are approved or cleared. The same reason applies to new indications for approved devices. It often takes payors months to determine whether or not to cover a new use or indication, and this can delay the actual availability of approved/cleared treatments to patients.

In addition, the FDA fosters early communications with payors, such as Centers for Medicare and Medicaid Services (CMS), through its Parallel Review Program that is intended to reduce the time between FDA marketing approval or clearance and CMS National Coverage Determinations. As part of that program, interested sponsors meet with FDA and CMS at various times to discuss the type of clinical evidence regarding medical devices that support positive decisions by each agency. Early input from payors regarding their evidentiary needs can streamline payor coverage and improve public health by facilitating earlier access to innovative, safe, and effective medical devices. The ability to freely share clinical information related to a device with a payor is a necessary element of available processes such as Parallel Review.

**Inclusion of Off-Label Data in Preparing Risk-Based Models for On-Label Uses**

Risk sharing is a key element of value-based healthcare, whereby manufacturers may partner with providers and/or payors to set a compensation model for devices based on certain outcomes-associated metrics. It requires the parties to develop models for risk sharing based on the outcomes associated with a device. Fundamental to these models is the creation of a baseline rate of outcomes for the patient population that will be treated with the device. This baseline is then used to determine whether the device usage improved outcomes, reduced readmissions, etc., and risk share payments are based on the results achieved. However, in some cases, developing the baseline may require consideration of both on-label and off-label information. For example, if a device is indicated to treat a certain stage of a disease, but the payor (or provider) covers patients with all stages of that disease, the payor may not be willing to separate out the different stages in setting the baseline or reviewing the changed outcomes. The payor or provider’s record system may not be set up to differentiate between stages of disease (e.g., it may record only “heart failure” and not stage I or II, III or IV) so that developing the baseline is impractical, or the payor may not be interested in drawing those distinctions among its patients. Since providers are free to use the device to treat patients at all stages of the disease, and the payor may pay for that, they will want to conduct the analysis for all stages of the disease. FDA policies should expressly recognize device manufacturers’ ability to develop such models necessary for such risk share agreements.
Restricting manufacturers from sharing comprehensive outcome data with providers and payors does not improve patient safety or further the public health. Rather, it simply hampers manufacturers’ and payors’ ability to engage in cost management and risk sharing activities that are part of new and innovative care models that HHS has been encouraging as a way to better manage healthcare spending, and interferes with efforts to utilize data analysis for treatment and payment decisions.

New On-Label Uses That Will Replace Off-Label Uses

Another situation to consider is when a new device is approved or cleared with an indication to treat a condition which was historically treated through the off-label use of another device. It may be necessary to provide payors with data on the safety and effectiveness profile of each device — the one used on-label and the one used off-label — in order to convince them to cover or otherwise encourage the use of the new device for its on-label indication. While this would involve providing information about an off-label use, the overall purpose is to gain coverage for an on-label use, and is consistent with FDA’s goals of evidence, transparency, and incentivizing use of products for their on-label indications.

Providing Information About Procedures That Include On- and Off-Label Data

In some cases, it may be helpful to provide payors with safety data related to a procedure type, including a mix of on- and off-label data. For example, payors often cover spinal implant procedures, regardless of the type of device used as the implant. The devices may be cleared or approved in connection with particular procedures, and also with specific indications, e.g., use only in certain levels of the spine. Where a new spinal implant procedure offers potential safety benefits — e.g., approaching the spine from the side, or the front, or the back — there is benefit in providing a payor with the available data on the adverse event/complication rate associated with the technique, even if that data includes procedures done at different levels of the spine than were approved for the particular implant device, or on patients with different pathologies listed in the device’s indications. These off-label data are meaningful to an assessment of the procedure.

Similarly, there may be situations in which a device is used to treat a condition, with a particular surgical approach (e.g., anterior vs. posterior approach). When providing economic information to a payor about using the device to treat a condition, the available data may involve different surgical approaches, both the approved and unapproved. This information may be of great value to the payor, which may cover the procedure regardless of approach and needs to understand the economic impact. Providing information about both surgical approaches is meaningful, and falls within the concept of “related to the approved indication” that is covered in the Food Drug and Cosmetic Act and FDA identified in its Payor Communications Draft Guidance. It is analogous to FDA’s discussion of dosages in the Payor Communications Draft Guidance, which references the ability to provide data on “actual patient use of an approved dosage form and strength of a drug for an approved indication [that] falls outside the recommended dosing regimen in the label, such as by taking at a different frequency or a different total dose than recommended.”
Manufacturers should be permitted to present factual materials that assess surgical techniques that are “agnostic” as to the device used, and that may include information on both on and off-label usage, but where the purpose of the presentation is not to promote a particular off-label use but rather to enable payors to evaluate a particular procedure for which the manufacturer’s device is indicated.

*Payor and value-driven healthcare requirements provide significant incentives for medical device manufacturers to develop high-quality data regarding unapproved uses* [Questions 2.a, 2.b; also see earlier comments regarding potential value of real-world evidence]

In the current healthcare environment, reimbursement decisions – regarding both medical devices and related procedures – play a critical role in determining the commercial viability of individual medical devices. The demand from payors and other healthcare stakeholders for high-quality safety, effectiveness, and value data to facilitate their decisions creates significant incentives for medical device manufacturers to develop and disseminate such data.

The financial burden associated with data development needed for FDA approval or clearance for additional uses of already approved or cleared devices has historically been an impediment to manufacturers. However, as medical device manufacturers are increasingly driven to generate robust data to address the demands of payors and other healthcare system decision makers and suppliers (e.g., hospital administrators and budget committees), the likelihood may increase that FDA approval or clearance for additional product uses can be supported with real-world information. In this regard, FDA’s increasing recognition of the value of real-world evidence in supporting regulatory submissions significantly enhances the likelihood that data generated can be leveraged to support additional submissions to FDA while fostering high quality, efficient, and value-based care. *See generally Real-World Evidence Draft Guidance.*

*As FDA recognizes, the nature of medical devices and scope of medical device data requires that a flexible standard be applied to assess evidentiary support for truthful, non-misleading statements* [Question 4, 4.b., 5.e, 6]

Significant and legitimate rationales exist for medical device manufacturers to employ various forms of communications regarding unapproved uses of approved or cleared medical devices, and these communications support various public health aims. AdvaMed agrees with FDA that it is critical that the information provided in these communications meet standards of scientific integrity. FDA has long recognized, however, that in light of the range and breadth of medical devices – and the type of data that may support their use – a flexible standard is appropriate for determining what constitutes sound scientific evidence.

Although randomized controlled trials – which are common in the pharmaceutical industry – are often viewed as the most robust means of assessing a medical product’s safety and effectiveness, FDA has recognized that such trials “may be impractical or challenging to conduct” in the medical device space. *See Real-World Evidence Draft Guidance* at 7. In particular, “the realities of medical device innovation and development cycles, ethical issues that may arise with treatment assignment,” *id.*, and other similar issues may make such trials impracticable or
impossible. Not only are traditional trials more challenging in the device space, but other types of scientific evidence, including more varied clinical data as well as real-world data, may provide legitimate and important sources of knowledge. Indeed, FDA has recognized that “a wealth of data covering medical device experience exists and is routinely collected in the course of treatment and management of patients.” See Real World Evidence Draft Guidance at 5. This reality is also reflected in FDA’s existing standard for assessing whether “valid scientific evidence” exists to establish the safety and effectiveness of a device under approval review. Examples of “valid scientific evidence” identified by FDA include “evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a . . . device . . . .” 21 C.F.R. Part 860.7(c)(2).

As a key feature of FDA’s device program, the scientifically grounded and flexible evidentiary standard of “valid scientific evidence” should be similarly adopted for assessing whether unapproved use information is scientifically appropriate to communicate to healthcare professionals. FDA has already, and should continue to, recognize the value of varying types of scientific information regarding medical devices.

AdvaMed urges FDA to apply this standard meaningfully in the context of communications regarding unapproved uses of approved or cleared medical products by ensuring that the full range of scientific information per FDA statute and regulation be permitted for communication. We note that types of medical device scientific information that may be scientifically sound sources of support for communications regarding unapproved uses of approved or cleared products include retrospective analyses; observational data; patient registries; meta-analyses; post-hoc analyses; and well-designed bench or animal studies particularly when clearance or approval is based upon bench or animal studies. In addition, as recognized in the “valid scientific evidence” definition, in appropriate circumstances, sound scientific data may come in the form of “well-documented case histories conducted by qualified experts, and reports of significant human experience” with a particular medical device. 21 C.F.R. Part 860.7(c)(2).

AdvaMed members recognize that sound scientific evidence is information developed using generally-accepted scientific standards appropriate for the information being conveyed that yield accurate and reliable results. As discussed below, communications should include appropriate disclosures of any limitations in the data and analytical methodologies to permit audiences to independently assess the robustness of the data.

As previously discussed in our comments, experience in the field following marketing approval or clearance may provide critical safety or effectiveness information (e.g., relates to device placement and use in combination with other products). In addition safety studies mimicking clinical scenarios with *in vitro* or *in vivo* models can provide valuable information to assess the benefits versus risk of a new use. Facilitating responsible, scientifically accurate discussion of this type of information therefore may allow healthcare professionals greater access to important safety and effectiveness information. Communications with healthcare professionals and other stakeholders regarding real-world observations may also be critical during the early development of a device or application of an approved device to a new use. Ultimately, patients benefit as
allowing medical device developers to better leverage existing evidence and reducing the cost of clinical trials can lead to more timely introduction of safe and beneficial technologies for patients.

In addition, AdvaMed notes that a requirement that medical product manufacturers limit their dissemination of scientific information to only peer-reviewed publications, such as journal articles, reference texts, or clinical practice guidelines, would be overly narrow and would not meet the needs of stakeholders, including healthcare professionals and payors. Drafting and publishing a manuscript can take substantial time, even years for some prestigious journals. These timetables may make peer-reviewed publications an impracticable means of disseminating timely information regarding emerging uses of approved medical products. Manufacturers may also not publish all scientifically sound data in peer-reviewed publications for a number of reasons. For example, a journal may reject a manuscript even where the manuscript describes robust data because the journal determines that other manuscripts are of more interest to the journal’s readers.

Moreover, not all information of interest to a healthcare professional or payor will be directly addressed by existing peer-reviewed journal articles, reference texts, or clinical practice guidelines. In some instances, a healthcare professional or payor may be interested in a particular aspect of the data or the device itself that was not the focus of a publication. In this regard, there may be scientifically sound unpublished bench data that may be on file with a manufacturer and contains information relevant to safe and effective use of medical products. Manufacturers should be able to provide requesters with already available, scientifically valid data rather than be required to develop a new manuscript, submit for peer-review, and wait for final publication before disseminating scientifically sound information. Without such flexibility, manufacturers may hesitate to provide healthcare professionals with available, relevant, and scientifically sound information that facilitates the safe and effective use of medical products.

On the other end of the spectrum, in some cases there may be dozens or more publications available that relate to a specific use of a medical device. As previously discussed, the average physician does not have the time or ability to review that volume of publications in depth. In these situations, allowing manufacturers the flexibility to draft an accurate, truthful and non-misleading summary, with appropriate disclosures, and provide it to interested parties benefits not only the physicians who gain education in this way, but also the patients they are able to help as a result.

Accordingly, AdvaMed urges FDA to expand its Distributing Scientific and Medical Publications Revised Draft Guidance to further acknowledge the varying types of scientific information regarding medical devices that reflect valid scientific evidence appropriate for distribution with the associated controls specified in that guidance, as well as explicitly allow for fact-based summaries of the available valid scientific evidence.

AdvaMed believes that manufacturers should be permitted to disseminate communications based on data that is scientifically valid, regardless of whether that data is publicly available. To advance this aim, AdvaMed would support the following actions by manufacturers for
communications that utilize non-public data regarding unapproved uses of approved or cleared medical products: (1) maintaining on file any non-public data relied upon in such statement, and (2) providing additional supporting data upon request by a healthcare professional or other stakeholder.

Finally, AdvaMed does not propose specific circumstances in which it is appropriate for medical product manufacturers to communicate with patient and consumer audiences, or the standard that should be applied in evaluating such communications. We recognize, however, that patients – particularly those for whom limited treatment options may exist – may have a strong interest in learning about potential treatments, which may include unapproved uses of approved and cleared medical products. Indeed, in the internet age, patients have become more engaged in evaluating available medical options and participating in making decisions regarding their treatment.

Truthful and non-misleading communication can play an important role in helping address unmet needs for information about emerging healthcare advances regarding serious and life-threatening conditions, rare disease, and personalized medicine.

For these reasons, foreclosing the possibility that manufacturers may engage in truthful, accurate communications regarding unapproved uses that are appropriate for patient audiences could be harmful for patients and, at a minimum would limit their ability to be active participants in their own healthcare. In this regard, AdvaMed notes that FDA has previously recognized that it is possible to differentiate between healthcare professional and consumer audiences in assessing whether a particular communication is non-misleading to its intended audience. See FDA Draft Guidance for Industry – Presenting Risk Information in Prescription Drug and Medical Device Promotion, at 6. (“Due to their training and experience, healthcare professionals develop a level of knowledge related to scientific concepts and medical conditions and products that lay consumers do not possess. FDA takes this difference in knowledge and experience into account when assessing promotional materials directed at healthcare professionals versus those directed at lay audiences.”) AdvaMed believes a similar distinction could be drawn in this context. In particular, AdvaMed recognizes that the type of information and disclosures that may be non-misleading for healthcare professionals with a deeper understanding of clinical trial design and the potential limitations of different types of studies may not always be appropriate for patient audiences. See, e.g., Gita Venkatarmani Johar and Carolyn Simmons, The Use of Concurrent Disclosures to Correct Invalid Inferences, 26 J. CONSUMER RESEARCH 307 (2000) (finding that highly motivated respondents were more likely to discern the main claims using concurrent disclosure in ads).

Various means exist to ensure that communications based on valid scientific evidence are truthful and non-misleading [Question 5, 5.a, 5.c, 5.d]

AdvaMed acknowledges that there are a broad range of communications and activities in which medical device manufacturers participate, and the data that support these communications falls across a continuum of scientific information. AdvaMed stands ready to work with FDA to assess a means of ensuring that healthcare professionals have the tools necessary to evaluate the quality of data supporting manufacturer communications. AdvaMed believes that appropriate
disclosures can play a key role in supporting truthful and non-misleading communications by providing healthcare professionals with information necessary to assess these communications.

AdvaMed agrees with FDA’s suggestion in the Agency Memorandum that, in certain circumstances, disclosures alone may not be “sufficient to prevent harm or deception.” See Agency Memorandum at 29. First and foremost, disclosures may never be sufficient to overcome limitations in the communications when the information being communicated is false or if the information does not meet standards of scientific integrity. However, where the communications are based on valid scientific evidence, AdvaMed believes that appropriately crafted disclosures play a valuable role in ensuring that manufacturer’s communications do not present a misleading impression and can be properly assessed by healthcare professionals.

FDA, other federal agencies, and the courts all have recognized the value of appropriate disclosures in preventing communications from being misleading. In the medical device space, for example, FDA recognizes that disclaimers may assist users with assessing data quality for devices approved under CDRH’s Expedited Access Pathway (EAP) Program for medical devices, under which FDA may approve a device with a higher degree of uncertainty about benefits/risks. As part of this EAP Program, FDA may impose conditions of approval on the device labeling “in order to ensure that patients and healthcare providers have complete and accurate information regarding what is known about the benefits and risks of the device,” such as including in the labeling a succinct description of the uncertainty about anticipated benefits/risks and the extent of data that supported approval. *FDA Guidance - Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions* (April, 2015). As another example, the FDA Regulatory Procedures Manual provides that FDA districts will generally permit the display at trade shows of imported devices that are not approved or cleared where a placard is used at the point of display advising that the product may not be in compliance with applicable FDA regulations. *FDA Regulatory Procedures Manual*, Chapter 9-16.

FDA also has widely accepted the use of disclosures in connection with other medical products. For instance, disclosures are used prominently in the dietary supplement space. *FDA Dietary Supplements Labeling Guide: Chapter VI. Claims*. Similarly, FDA has long encouraged the use of various disclosures to guard against misleading distributions of medical journal articles and medical and scientific reference publications on unapproved uses of approved or cleared medical products. See generally *Good Reprints Practices Guidance; Distributing Scientific and Medical Publications Revised Draft Guidance*).

The Federal Trade Commission (“FTC”), which has authority over the advertising of unrestricted medical devices, has informative and robust guidance on how to make disclosures clear and conspicuous, endorsing the use of disclosures to “qualify or limit a claim to avoid a misleading impression.” *FTC, .com Disclosures: How to Make Effective Disclosures in Digital Advertising* (Mar. 2013) at 5. These guidelines provide that “disclosures that are required to prevent an advertisement from being deceptive, unfair, or otherwise violative of [an FTC] rule, must be presented ‘clearly and conspicuously’.” *Id.* The guidelines further explain that “[i]f a disclosure is necessary to prevent an advertisement from being deceptive, unfair, or otherwise violative of
[an FTC] rule, and if it is not possible to make the disclosure clear and conspicuous, then either the claim should be modified so the disclosure is not necessary or the ad should not be disseminated.” Id. AdvaMed believes that similar concepts could be successfully employed to ensure that communications regarding unapproved uses of approved or cleared medical devices are not misleading. The use of disclosures to guard against misleading impressions has also been recognized by courts that specifically considered the issue with regard to FDA-regulated products.

AdvaMed believes that the type of manufacturer communication should be taken into account when creating the framework for the types of disclosures needed to ensure that the particular communication is not misleading to the specific audience. While we do not take a position on specific disclosures that would be appropriate for particular types of communications, we believe that examples of appropriate disclosures for manufacturer affirmative or promotional communications that include unapproved uses of approved or cleared medical products could include the following, as appropriate:

1. Identification that some or all uses of the manufacturer’s drugs or devices described in the information have not been approved or cleared by FDA.

2. Whether the manufacturer is seeking approval/clearance for the particular use, or, if appropriate, that the manufacturer has sought and been denied approval for the particular use and the reason for the denial.

3. Disclosure of any authors known to the manufacturer as having a financial interest in the manufacturer or in a product of the manufacturer, if such information is not already disclosed in the information disseminated.

4. If not specifically referenced in the communication, significant risks or safety concerns associated with the unapproved use(s) of the manufacturer’s product(s) discussed in the communication that are known to the manufacturer and have not been fully investigated by the manufacturer and determined to be related to such use.

FTC guidance provides helpful guidance for determining both the manner in which disclosures should be made and how to assess whether disclosures are effective. For example, the FTC has specifically addressed how disclosures should be formatted on internet sites and in social media activity. See generally, FTC,.com Disclosures; FTC, Native Advertising: A Guide for Businesses (December 2015). Moreover, much like FDA’s approach in its Presenting Risk Information Draft Guidance, the FTC provides that whether a disclosure meets the required standards “is measured by its performance — that is, how consumers actually perceive and understand the disclosure within the context of the entire ad. The key is the overall net impression of the ad — that is, whether the claims consumers take from the ad are truthful and substantiated. If a disclosure is not seen or comprehended, it will not change the net impression consumers take from the ad and therefore cannot qualify the claim to avoid a misleading impression.” FTC,.com Disclosures at 6. AdvaMed urges FDA to consider adopting similar,
commonsense principles for evaluating disclosures in the context of communications regarding unapproved uses of approved or cleared medical products.

Amidst increasing availability of information and demand for accurate, scientifically grounded information, the medical device industry takes seriously its responsibility to engage in truthful, non-misleading communications [Questions 3, 4.a, 5.a, 5.b, 8]

AdvaMed members take seriously the importance of ensuring that information they communicate is accurate and scientifically grounded. We recognize that information that is not truthful or accurate undermines the public health, but we believe that safeguards are in place to guard against this type of information. Medical device manufacturers endeavor to ensure that communications regarding unapproved uses of their approved or cleared products are truthful, non-misleading, and scientifically sound, and include information necessary to facilitate the communication being understood by the recipient. As part of those efforts, medical device manufacturers engage in rigorous evaluation of such information prior to dissemination to ensure that it meets these standards.

This evaluation typically takes the form of comprehensive reviews of proposed communications, oftentimes by cross-functional committees that include representatives from the manufacturer’s medical or scientific, legal, and regulatory departments. These reviews are focused on evaluating whether a product-related communication is supported by valid scientific evidence, as well as whether the communication is truthful and non-misleading.

In many companies, the process employed for evaluating communications regarding unapproved uses of their products (e.g., in response to unsolicited requests for information or distribution of peer-reviewed articles) is as rigorous as that employed to ensure that promotional communications regarding approved uses comply with FDA regulations and guidance, for example, with respect to fair balance. Companies utilize various mechanisms to ensure that these reviews are appropriately robust. For example, companies may create detailed internal guidance documents used by review committees in evaluating product-related communications, create dossiers of scientifically valid evidence supporting various product information or claims, and routinely train committee members on evolving regulatory and scientific standards. Moreover, the medical and scientific personnel who participate in company reviews of product communications generally have significant expertise in the relevant therapeutic areas. These personnel take seriously their obligations to review communications relating to both approved and unapproved uses and to employ their medical and scientific expertise to ensure the communications’ scientific validity.

As discussed earlier in our comments, we appreciate that recent FDA draft guidance documents address aspects of communicating information that does not explicitly appear in the product label but may be consistent with the FDA-required labeling. As critical to this effort, we encourage FDA to provide optimal clarity through a clear definition for information related to unapproved uses of approved or cleared medical products to cover additional types of communications that may be consistent with FDA-required labeling as they do not create a new intended use. This is because many of the communications that medical device manufacturers consider making
involve information that pertains to a use that has been approved or cleared by FDA but does not explicitly appear in the approved product labeling (for a device subject to premarket approval) or statement of intended uses (for a device subject to premarket notification).

**FDA should not proceed with implementation of the final tobacco rule as drafted, which has been subject to a one-year delay and represents a significant and unwarranted expansion of the definition of intended use and creates substantial uncertainty for regulated industries as well as due process concerns.** [Question 8.a].

In a similar vein, AdvaMed is pleased FDA has decided to reconsider and further delay the implementation of the final rule proposed in its January 9, 2017 notice of final rulemaking (82 Fed. Reg. 2193, delayed at 82 FR 9501 on February 7, 2017), which revised the definition of “intended uses” in 21 C.F.R. § 801.4. The final rule adopted a significantly different definition than initially described by the Agency in the proposed rule on September 25, 2015 (80 FR 57756). More specifically, the proposed rule would have deleted from the definition of “intended uses” currently in 21 C.F.R. § 801.4 the following: “But if a manufacturer knows, or has knowledge of facts that would give him notice that a device 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 device which accords with such other uses to which the article is to be put.” By contrast, the final rule replaces that statement with the following: “And if the totality of the evidence establishes that a manufacturer objectively intends that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than ones for which it has been approved, cleared, granted marketing authorization, or is exempt from premarket notification requirements (if any), he is required, in accordance with section 502(f) of the Federal Food, Drug, and Cosmetic Act, or, as applicable, duly promulgated regulations exempting the device from the requirements of section 502(f)(1), to provide for such device adequate labeling that accords with such other intended uses.”

The definition of the final rule raises important substantive concerns and, given the significant difference from the proposed rule, was adopted without notice or meaningful opportunity to comment. The rule should be stayed indefinitely and reconsidered by FDA. Such regulation runs counter to the long-established concept of “intended use” and represents a drastic change from the proposed rule. The “totality standard” set in the final rule, if finalized, would represent a significant and unwarranted expansion of the definition of intended use and creates significant uncertainty for regulated industries as well as due process concerns. We will provide fuller comments to the docket in response to the request for FDA comments, but we raise this issue in need of foremost address. The original proposal had been widely supported, and we urge FDA to return to its original proposal.
Policies should clearly articulate and safeguard—and not create unnecessary hurdles or impose a pre-review regime—for manufacturers’ truthful, non-misleading, scientifically valid communications regarding unapproved uses of approved or cleared medical products, which may substantially advance the public health. FDA should also promulgate regulation to clearly define scientific exchange [Questions 3, 5.b, 7, and 8]

Given the seriousness with which medical device manufacturers approach their obligation to provide truthful, non-misleading information to healthcare professionals and other key stakeholders and the federal and state authorities that exist to address false and misleading communications, AdvaMed urges FDA to outline a clear policy that safeguards such appropriate communications and provides a safe harbor from FDA enforcement action. AdvaMed also believes adoption of a pre-review regime for communications regarding unapproved uses of approved or cleared medical devices is unnecessary, and more importantly, would not advance public health interests. To the contrary, such regime would significantly delay and impede manufacturers’ ability to provide truthful, non-misleading, scientifically sound—and timely—information to healthcare professionals and other stakeholders compounding the impediments to dissemination of truthful and non-misleading information on unapproved uses that already exist in the current environment. Furthermore, medical device manufacturers may abstain from engaging in communications regarding unapproved uses of their approved or cleared devices when those communications would greatly benefit the public health.

Similarly, medical device manufacturers frequently engage in appropriate activities regarding unapproved uses of approved or cleared products in support of scientific exchange. As previously outlined in comments to FDA, these communications may include presentations at educational and medical meetings regarding clinical trial results or research and development data for an investigational use, discussions with healthcare professionals to obtain advice or feedback relating to investigational research and development, and discussions with consultants such as during advisory boards. These communications are critical to the continued development, iteration, and evolution of medical devices in support of serving the public health and treating patients with unmet medical needs. FDA should take care to ensure that any policy does not chill scientific exchange nor engagement in truthful, non-misleading communications in support of these and other types of activities that support scientific discourse and the overall public health.

In order to ensure robust and full exchange of scientific discourse in the benefit of the public health, AdvaMed encourages FDA to provide more clarity on communications and activities that constitute “scientific exchange.” Furthermore, we believe that FDA should clearly recognize a firm’s ability to engage in scientific exchange outside of the investigational context.

CONCLUSION

AdvaMed appreciates the opportunity to provide these comments on this important topic. We support FDA’s efforts to review its policies regarding manufacturer communications on unapproved uses of approved and cleared medical products and to consider stakeholder views in this regard. As FDA has been considering its policy on this and related questions for some
period of time, we have attached our prior comments on the relevant topics of scientific exchange and responding to unsolicited requests regarding new and unapproved uses (see Attachment A and Attachment B). We hope these comments will be of additional assistance to FDA in completing its review of this critical topic.

In the medical device space in particular, the healthcare environment is rapidly changing and product development and innovation is occurring at a breakneck pace. The need for stakeholder access to truthful and non-misleading product information has never been greater. For example, as FDA recognizes in Question 3 of the FR notice, a broad variety of information about medical products is now available from a wide variety of sources. Unfortunately, not all of the publicly available information is accurate and the data supporting such information varies significantly in scientific quality. Medical device manufacturers are often uniquely well-situated to provide up-to-date, comprehensive and accurate information regarding both approved and unapproved uses of their products, but may hesitate to publicly correct misinformation or provide higher quality data regarding what may be seen as unapproved uses. Facilitating these types of truthful, non-misleading communications in appropriate circumstances can substantially support the public health and promote access to quality scientific information.

Clear Agency policy that ensures transparent and explicit recognition of truthful and non-communications regarding unapproved uses of approved and cleared medical products can play a critical role in supporting scientific progress and overall advances in high quality medical device technologies and efficient care for U.S. patients. To that end, AdvaMed emphasizes the importance of timely action. Simply put, the current lack of guidance is not in the best interests of the public health. Transparent Agency policy articulated in guidance documents that safeguards appropriate manufacturer communications consistent with the First Amendment will facilitate research on new and innovative uses of existing medical devices, development of new devices, promote robust clinical evaluation of medical devices, and support the overall effectiveness of the healthcare system.

Best Regards,

/s/

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