Early January has seen the release by FDA of a flurry of information on drug and device manufacturer communications, largely reaffirming FDA’s long-held approach to restricting manufacturer communications regarding off-label uses of approved drugs and medical devices. The most significant positive development arising from these documents is the Agency’s concession on proactive pre-approval communications with payors about investigational drugs and devices, allowing certain information to be provided to payors prior to a product’s approval. FDA’s guidance documents issued this week also clarify some grey areas surrounding the circumstances under which manufacturers may communicate about information that is consistent with or related to an approved indication, but is not included in approved product labeling.
While these pronouncements provide drug and device manufacturers with some additional leeway in their communications regarding investigational products and certain information about the approved uses of their products that is not included in the approved labeling, they do not address long-standing questions regarding the circumstances under which manufacturers may communicate about unapproved uses of their products in light of recent First Amendment case law. Instead, these last words of the Agency under the outgoing administration signal that, at least under the direction of current administration, FDA is not inclined to significantly expand manufacturers’ ability to communicate regarding unapproved uses of their products without the risk of enforcement. The eventual impact of the new administration on FDA’s approach to off-label communications remains a significant unknown.

In draft guidance on Drug and Device Manufacturer Communications with Payors, Formulary Committees and Similar Entities – Questions and Answers released on January 18, FDA signifies its acceptance of the position long held by industry and payors alike that payors need access to information regarding investigational drugs and devices to help them plan and budget for coverage of these products once they are approved. In the draft guidance, FDA states that it will not object to manufacturers providing payors with “unbiased, factual, accurate and non-misleading” information regarding investigational drugs and medical devices, provided that those communications include a clear statement of the investigational status of the product and that its safety and effectiveness have not been established, along with information regarding the stage of product development of the product.

Information that may be provided by manufacturers in accordance with FDA’s recommendations in the draft guidance includes information about the product such as its drug class or design, the indication sought and the patient population under investigation, a factual presentation of the results of clinical and pre-clinical studies without any conclusions regarding the product’s safety and effectiveness, the anticipated timeline for FDA approval, product pricing information, and anticipated marketing strategies and product-related programs and services, such as patient assistance programs. FDA also recommends that manufacturers update payors with any significant new information about the investigational product that differs from information previously communicated to them.

As suggested by its title, the primary focus of the draft guidance is on the communication of health care economic information (“HCEI”) regarding prescription drugs to payors, interpreting the changes to FDAMA Section 114 included in the 21st Century Cures Act that was signed into law in December. Notably, unlike FDA’s recommendations regarding pre-approval product communications with payors, this portion of the draft guidance does not apply to HCEI regarding medical devices. The draft guidance also makes it clear that the expanded HCEI communications permitted by FDAMA 114, as amended, are limited to payors, and similar flexibility in the levels of evidence required to support HCEI communications to payors do not apply to communications with health care providers or consumers. Additionally, consistent with the statute, the draft guidance limits the HCEI that may be provided to information that “relates to” an approved indication, confirming that FDA does not currently intend to permit the proactive dissemination to payors of HCEI related to off-label use.
In a series of questions and answers, FDA provides recommendations regarding the types of HCEI that may be provided, the scope of the payor audience to which this information may be provided, the types of competent and reliable scientific evidence that may be relied upon, the information that must be disclosed along with HCEI provided to payors, and perhaps mostly usefully, examples of the circumstances under which FDA will determine HCEI to relate, and not to relate, to an approved indication. FDA describes the categories of information that will be deemed to relate to an approved indication, even if they do not appear within, or vary in some respects from, the approved labeling; provided that the information is not inconsistent with the approved labeling. These include, among others, information on duration of treatment, burden of illness, length of hospital stay, information including actual patient use of an approved drug that varies from the approved dosing regimen, and information derived from clinical data demonstrating an effect on a validated surrogate endpoint or a comparison of safety and effectiveness with another drug or intervention.

FDA's approach to “related” information in the draft guidance is similar to that taken in another draft guidance it released on January 17 on Medical Product Communications that are Consistent with the FDA-Required Labeling – Questions and Answers. In the Medical Product Communications draft guidance, FDA provides recommendations for manufacturers of drugs and medical devices on communications, including communications with health care providers, consumers and payors and in promotional materials, regarding information that is not included within the FDA-approved package labeling, but is consistent with that labeling.

In determining whether information provided by manufacturers is consistent with the product’s approved labeling, FDA will consider three factors. First, FDA will compare the information to the conditions of use in the approved labeling. To comply with the recommendations in the guidance, the information must relate to an indication, patient population, and dosing and administration instructions within the scope of those set forth in approved label, and it must not be inconsistent with any use limitation or directions for handling or using the product in the approved labeling. Second, the suggestions regarding the use of the product in the HCEI information must not increase the potential for patient harm relative to information in the approved labeling or otherwise adversely impact the risk-benefit profile of the product. Finally, the directions for use in the approved labeling must allow the product to be used safely and effectively under the conditions of use suggested in the HCEI information distributed by the manufacturer. If all three of these factors are met, FDA will not view that information, alone, as evidence that the manufacturer intends to promote the drug or device for a new intended use.

To assist manufacturers in applying these factors, the guidance includes examples of the types of communications that are, and are not, consistent with a product’s approved labeling. In describing the types of evidence required to support the disclosure of information that is not included in, but is consistent with, the approved labeling, FDA states that the data must be scientifically and statistically sound to support the representations made by the manufacturer to avoid being false or misleading, but because the safety and effectiveness of the product for the approved indication has already been established, the evidence need not meet the applicable approval or clearance standard for the product. For drug products, this means that
two adequate and well-controlled clinical trials will not be required. The evidence must, however, be accurately characterized and any material limitations on the evidence must be clearly and prominently disclosed in language appropriate for the intended audience.

FDA also has, within a ten day period, released two other pieces of information relating to drug and device manufacturers' communications regarding their products. On January 9, FDA issued a Final Rule on Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding “Intended Uses”, clarifying the Agency’s position that a determination of a regulated product’s intended use may be determined based upon the totality of the evidence of the manufacturer’s objective intended use of the product, including the manufacturer’s knowledge of the product’s actual use for an off-label indication in practice.\(^1\) FDA states in the preamble to the Final Rule, however, that it will not bring an enforcement action based solely on a manufacturer’s knowledge that an approved or cleared product is being prescribed or used for an unapproved use.

The Proposed Rule released in September 2015 deleted from the drug and device intended use regulations at 21 CFR §§ 201.128 and 801.4 a reference to a manufacturer’s knowledge of off-label uses, specifically the statement that “[Intended use] may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.” Many commenters on the Proposed Rule had interpreted that deletion as excluding a manufacturer’s knowledge of off-label use from the evidence that may be relied upon to establish a manufacturer’s intent to promote a drug or device for an off-label use. The preamble to the Final Rule expresses FDA’s disagreement, and clarifies that FDA proposed deleting that language merely to avoid a potential misinterpretation that a manufacturer’s knowledge of an unapproved use of an approved or cleared medical product, without more, automatically triggers a requirement for that manufacturer to provide additional labeling for the unapproved use. FDA asserts that its intent was not to change the scope of information that could be relied upon as evidence of a manufacturer’s intended use of the product. The amended language set forth in the Final Rule provides that “intended use may be shown, for example, by circumstances in which the article is, with the knowledge of such person or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.”

In the preamble to the Final Rule, in response to comments that existing First Amendment jurisprudence restricts FDA from bringing enforcement actions based on truthful and non-misleading speech regarding a product’s off-label use, FDA states that it is separately examining its rules and policies relating to firm communications regarding unapproved uses of approved and cleared medical products, and while those broader policy considerations are being addressed separately from the Final Rule, “[n]evertheless, it is important to note here that we do not agree with the assertion that the current case law allows FDA to consider speech as evidence of intended use only when it is false or misleading.” FDA cites recent Second Circuit precedent\(^2\) to support its view that the Second Circuit’s 2014 *Caronia* decision does not foreclose the government’s ability to prove misbranding using promotional
speech as evidence that a drug is intended for an off-label use. FDA goes on to
describe the significant public health considerations that the Agency believes
support its approach to limiting manufacturer communications regarding off-label
uses of their approved or cleared products.

FDA makes similar assertions in a document posted to the docket for the November
public hearing on Manufacturer Communications Regarding Unapproved Uses of
Approved or Cleared Medical Products entitled, “Memorandum: Public Health
Interests and First Amendment Considerations Regarding Unapproved Uses of
Approved or Cleared Medical Products.” In a notice published in the Federal
Register on January 19, 2017, FDA announces that it has reopened the comment
period that was opened in connection with the public hearing on off-label
communications that took place November 9 and 10, 2016 to allow interested parties
an opportunity for additional comment based on the content of the memorandum and
the two draft guidances discussed above. In this memorandum, FDA describes in
detail the public policy considerations guiding its assessment of its restrictions on
off-label communications, and the legal authority it believes supports its restriction
of these communications and their use as evidence of intended use to support
misbranding actions. FDA also describes its views on several alternative approaches
to addressing the public health interests at issue. FDA seeks additional comments
on its views expressed in the memorandum and potential alternative approaches to
regulating manufacturer communications regarding off-label indications of their
approved products. The docket will remain open until April 19, 2017.

[1] In addition to its provisions specific to determinations of when a tobacco product will be regulated as a
drug or device, the Final Rule also amended intended use regulations at 21 CFR §§ 201.128 and 801.4.


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