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ONE HUNDRED FIFTEENTH CONGRESS

Congress of the United States
House of Representatives

COMMITTEE ON ENERGY AND COMMERCE
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MEMORANDUM

July 10, 2017

To: Subcommittee on Health Democratic Members and Staff

Fr: Committee on Energy and Commerce Democratic Staff

Re: Hearing on "Examining Medical Product Manufacturer Communications"

On **Wednesday, July 12, 2017 at 10:15 a.m., in room 2322 of the Rayburn House Office Building**, the subcommittee will hold a legislative hearing on two discussion drafts relating to medical product manufacturer communications regarding unapproved uses of such products.

I. BACKGROUND

The Food and Drug Administration (FDA) has authority to prohibit the introduction of medical products into interstate commerce if the products do not meet the requirements for approval, licensing, or clearance, or are otherwise misbranded or adulterated. Medical products intended for uses that have not been approved or cleared by FDA are also prohibited, even if the same medical product was previously approved or cleared for another use. Intended use of a medical product can be established through the product's label, accompanying labeling, promotional claims, advertising, and any other relevant source.[1]

[1] Food and Drug Administration, *FDA Memorandum--Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products* (Jan. 2017) (file:///C:/Users/ssatchell/Downloads/FDA_Memorandum--Public_Health_Interests_and_First_Amendment_Considerations_Related_to_Manufacturer_Communications_Regarding_Unapproved_Uses_of_Approved_or_Cleared_Medical_Products_Jan_2017.pdf).

In order to be approved or cleared by the FDA for an intended use, a manufacturer must demonstrate that the medical product is safe and effective for that intended use. Manufacturers of medical products must demonstrate that the products are safe and effective. FDA will also review whether the product's intended use benefits outweigh the risks. Manufacturers may seek approval or clearance for new uses of a medical product by submitting a supplemental application demonstrating the new use is safe and effective.

Congress recognized long ago the importance of mandating that manufacturers provide data demonstrating the safety and efficacy of their medical product prior to marketing. [2] In the premarket review process, FDA requires manufacturers to generate reliable scientific evidence to demonstrate the safety and effectiveness for each new use of the medical product. Manufacturers must also develop "adequate directions for use" as a part of the product's labeling to support its safe and effective use.

It is common for a medical product to be used in a way that is not consistent with its labeling, such as to treat another disease, or for a population not studied for purposes of approval. It is estimated that one in five prescriptions written are for off-label uses; and, such uses may even be recommended in certain clinical practice guidelines.[3] Off-label uses, however, can still have serious public health implications.

Under current law, drug and medical device manufacturers can disseminate certain medical and scientific information regarding unapproved uses of approved drugs and approved or cleared medical devices to health care professionals and entities. Such information must be truthful and non-misleading, and may include scientific and medical reference texts, clinical practice guidelines, and journal articles. If such information is disseminated in accordance with FDA guidance[4], then it will not conclude that the manufacturer intends for the product to be used for an unapproved use. Manufacturers can also respond to unsolicited requests from health care professionals about unapproved uses so long as it is truthful, balanced, non-misleading, and non-promotional, and is done in response to a specific request.[5]

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[2] *See, e.g.*, Drug Amendments of 1962, Pub. L. No. 87-781 (1962)(Kefauver-Harris Amendments); Medical Device Amendments of 1976, Pub. L. No. 94-295 (1976).

[3] Department of Health and Human Services, Agency for Healthcare Research and Quality, *Off-Label Drugs: What You Need to Know* (http://www.ahrq.gov/patients-consumers/patient-involvement/off-label-drug-usage.html).

[4] Food and Drug Administration, *Guidance for Industry Distributing Scientific and Medical Publications on Unapproved New Uses —Recommended Practices, Revised Draft Guidance* (Feb. 2014) (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387652.pdf).

[5] Food and Drug Administration, *Guidance for Industry Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices, Draft Guidance* (December 2011) (https://www.fda.gov/downloads/drugs/guidances/ucm285145.pdf).

The 21st Century Cures Act further expanded the types of information manufacturers can share with payers and formulary committees regarding approved uses, to include health care economic data. The data can be any analysis that identifies, measures, or describes the economic consequences of the use of a drug and may include a comparison of the use of the drug to another drug, health care intervention, or to no intervention.

The Supreme Court has recognized that speech that aids pharmaceutical marketing is "a form of expression protected by the Free Speech Clause of the First Amendment."[6] Recent court decisions have prompted uncertainty, however, around which types of communication about unapproved uses are permissible. In *U.S. v. Caronia,* the U.S. Court of Appeals for the Second Circuit overturned a conviction of a pharmaceutical sales representative for off-label claims related to the use of a very rare disease product determining that the First Amendment's protection of commercial speech allowed for truthful, off-label promotion statements. However, the Second Circuit has also confirmed that "*Caronia* left open the government's ability to prove misbranding on a theory that promotional speech provides evidence that a drug is intended for a use that is not included on the drug's FDA-approved label."[7] Therefore, while FDA may not be able to prohibit the use of off-label promotion if it is truthful and non-misleading, such communication can be used as evidence of the manufacturer's intended use for the product and evidence as to whether the product is misbranded.

More recently, FDA has sought to reexamine its policies related to off-label communication. In November 2016 the agency held a public meeting and released additional guidance with the goal of "determining how best to integrate the significant and sometimes competing public health and safety interests served by FDA's regulatory approach related to unapproved medical products with ongoing developments in science and technology, medicine, health care delivery, and constitutional law."[8] The agency also released a memorandum detailing the public health implications and First Amendment considerations related to off-label communication. While FDA acknowledges that scientific or medical information regarding unapproved uses of a medical device may help health care providers make better decisions regarding treatment for a patient where no approved or cleared treatment exists, the agency also notes that off-label communication may diminish the incentive for manufacturers to seek approval for new uses of their products; "The legal requirement to generate appropriate evidence to demonstrate the safety and effectiveness of medical products for each intended use creates the impetus for firms to conduct those studies for subsequent uses of products – studies that no other actor will likely have the motivation and resources to undertake."[9] FDA also noted in its memo

[6] *See* Sorrell v. IMS Health Inc., 564 U.S. 552 (2011).

[7] *See* U.S. ex rel. Polansky v. Pfizer, No. 14-4774 (2d Cir. 2016).

[8] Food and Drug Administration, *Memorandum: Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products* (Jan. 2017) (https://www.regulations.gov/document?D=FDA-2016-N-1149-0040).

[9] *Id.*

the potential for patient harm related to promotional activities and communications of unapproved uses of medical products, "Marketing activities and communications regarding the safety and effectiveness of a medical product for a particular use that are not properly supported by scientific evidence may thus create a false or misleading impression about the safety and efficacy of the medical product for that use, which can lead to prescribing or use decisions that harm patients."[10] The agency further details examples where a manufacturer's marketing or promotional activities caused harm to patients, and outlines alternative approaches to regulating off-label communications.

The draft guidances, released by FDA in January 2017, attempt to clarify the types of communications that are permissible. The first guidance entitled, "Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities -- Questions and Answers", addresses questions relating to dissemination of health care economic information by drug manufacturers to formulary committees about approved drugs, as well as communication about unapproved uses of drugs and medical devices.[11] The second guidance, entitled "Medical Product Communications That Are Consistent With the FDA-Required Labeling", discusses the agency's thinking related to manufacturer communications about data and information related to the approved or cleared uses of drugs and medical devices that is not included in the product's labeling. The agency also outlines factors it will consider when determining if a communication is consistent with the medical product's labeling.[12] Labeling is defined as either labeling FDA has reviewed or approved, or that provides adequate directions for use. The comment period for these two draft guidances closed on April 19, 2017.

Also in January, FDA finalized a rule clarifying how intended use will be determined. The agency reiterated that it will rely on "any relevant source of evidence on intended use" and "where the totality of the evidence is sufficient to establish a new intended use for a medical product, relevant provisions of the [Federal Food, Drug & Cosmetic Act] and its implementing regulations will be triggered."[13] The new Administration has delayed implementation of the final rule until March 2018.

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[10] *See* Note 1.

[11] Food and Drug Administration, *Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities –Questions and Answers Guidance for Industry and Review Staff, Draft Guidance (Jan. 2017)* (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537347.pdf).

[12] Food and Drug Administration, *Medical Product Communications That Are Consistent With the FDA-Required Labeling —Questions and Answers Guidance for Industry, Draft Guidance* (Jan. 2017) (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm537130.pdf).

[13] Food and Drug Administration, *Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to*

II. LEGISLATION

A. H.R. ___, Regarding Communications Regarding Intended Uses of Drugs and Devices; Scientific Exchange

The discussion draft released by Rep. Griffith (R-VA) would limit the types of evidence FDA could use when determining an intended use. The draft specifically prevents FDA from considering non-public statements about a medical product that is not reflected in any claim, promotional statement, material, or the circumstances relating to the distribution of such product, as well as any scientific exchange as a part of the scientific exchange safe harbor established in the proposal. The discussion draft would also create a scientific exchange safe harbor that would allow a manufacturer to communicate about an unapproved used of a drug or medical device if the communication is supported by competent and reliable scientific evidence, provides contextual information relating to the data, and discloses that the information has not been approved for purposes of labeling under the Federal Food Drug and Cosmetic Act.

B. H.R. ___, Regarding Facilitating Exchange of Information Prior to Approval

The discussion draft released by Rep. Guthrie (R-KY) would allow drug and device manufacturers to communicate health care economic information or scientific information to a payor, formulary, technology review committee, or other entity about an unapproved use of a drug or device. In order to make these types of communications, the manufacturer must intend to submit a supplemental application containing information that is based on competent and reliable scientific evidence. Such information must be based on study or studies the sponsor anticipates being sufficient to support approval and must include a statement regarding any material differences between the information provided and the labeling approved. However, such communication cannot be considered false, misleading, a form of misbranding, or a violation under FDA's premarket review authorities.

III. WITNESSES

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Regulations Regarding "Intended Uses"(Jan. 9, 2017) (https://www.federalregister.gov/documents/2017/01/09/2016-31950/clarification-of-when-products-made-or-derived-from-tobacco-are-regulated-as-drugs-devices-or).

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