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FDA-2017- N-5319

VIA ELECTRONIC SUBMISSION

January 10, 2018

Division of Dockets Management (HFA-305)

Food and Drug Administration

5630 Fishers Lane, Rm. 1061

Rockville, MD 20852

Re: Docket No. FDA-2017- N-5319 Public Hearing on Devices Proposed for a New Use with an Approved, Marketed Drug

Dear Sir or Madam:

The Combination Products Coalition (“CPC”)¹ welcomes the opportunity to offer comments on FDA’s Federal Register Notice entitled “Devices Proposed for a New Use with an Approved, Marketed Drug” dated September 26, 2017 and the Public Hearing held on November 16, 2017.

The CPC applauds the Agency’s efforts to re-examine the challenges faced by the medical products industry related to cross-labeled combination products, as defined in 21 CFR 3.2(e), and more specifically, products that are not able to achieve regulatory approval as cross-

¹ The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with FDA on issues affecting combination products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad and unique perspective to these issues.

labeled combination products due to a lack of cooperation between the manufacturers of separately supplied drug or medical device products.

The CPC previously provided comments on this topic as part of a conference held in May 2005 by FDA and the Drug Information Association. The CPC references Ms. Danelle Miller and Ms. Anna Longwell's presentation, "FDA's Role in Encouraging Innovation in Combination Products" and the accompanying meeting transcript located on the Agency's Combination Products Webpage².

The CPC has examined FDA's proposal on "Devices Referencing Drugs" ("DRDs") and this document contains the coalition's comments for the Agency's consideration. Overall, the CPC believes that the current proposal of using the medical device Premarket Approval ("PMA") pathway to approve new drug claims raises a number of outstanding practical, regulatory, and legal questions that must be resolved prior to the Agency implementing such an approach. These considerations are further described within the below sections.

I. Cooperation Between Device and Drug Manufacturers

The CPC strongly believes that cooperation between drug and device companies is preferred when those companies are engaged in development activities which may affect a conceived or already approved medical product of different classes (i.e. drug, biological product, or device). Each company serves as the domain expert on the technology, risks, and benefits associated with the drug-device system, and collaboration between companies maximizes the opportunity for development of a safe and effective product. Practically, however, cooperation between drug and device companies is often a requisite to developing the data and labeling necessary to ensure an approvable drug-device system.

The CPC recognizes that there are many devices intended for concomitant use with drug classes (e.g., low protein absorbing IV sets, insulin and other infusion pumps with programmable

² FDA/DIA Cross Labeling Workshop on May 10, 2005: Combination Products and Mutually Conforming Labeling, <https://www.fda.gov/CombinationProducts/MeetingsConferencesWorkshops/ucm116623.htm> (last visited Dec. 18, 2017).

features for drug types, anesthesia machines intended for certain anesthetics, etc.), and that there are conventional drug company-supplied devices kitted (or cross-labeled) with branded drugs that have a long history of safe and effective use. However, when a device company seeks to develop a device for a branded drug, there are significant regulatory challenges, deeper scientific questions, and legal obstacles that could be impracticable without a cooperating drug partner. For example, if a DRD company desired to use a branded drug for a new indication and/or a new route of administration, a host of concerns would be raised that may not be effectively addressed without the study of the drug to re-assess safety and effectiveness for the for a new indication or route. The level of complexity associated with drug studies and the inherent need to leverage previous non-clinical and early phase studies make it unlikely that a DRD sponsor would be successful without the drug company's cooperation.

Regardless of the proposed DRD, a drug company, as an expert in the drug's physicochemical characteristics and its mechanism of action, may have a number of valid reasons why it would not want to cooperate with a DRD company. These include, but are not limited to:

- The drug company may determine that the benefit/risk of a new indication/route of administration is not acceptable for market entry.
- The drug company may not have sufficient resources to divert from other more promising drugs in development to support or effectively cooperate with the DRD company, even though it sees some potential benefit to patients.
- The drug company may be concerned with the risk of product liability deriving from the combined use of the drug and device. Typically, the drug company would not want to encourage any alternative uses that are out of its control or may impact the drug's safety profile.
- The drug company may desire to develop its own delivery device or have existing commitments to another device partner and would prefer not to support a competitive or inferior technology.

Although FDA’s proposal intends to increase patient access to therapies, it runs the risk of discouraging cooperation between drug and device sponsors, as it provides DRD companies and FDA reviewers with additional confidence that they may pursue new drug-related claims for separately supplied medical devices without the consent of the drug company. In circumstances where the drug company does not desire to collaborate, FDA may be inadvertently creating a pathway to market that would not have otherwise existed.

As FDA stated within the proposal, cooperation between companies is the preferred pathway for labeling separately supplied medical products for combined use. The CPC believes the most advantageous pathway to achieve collaboration between drug and device companies is to incentivize the drug company to participate in the device approval process. The CPC believes it is unlikely FDA could create sufficient incentives without a congressional mandate or new law. Congress could encourage cooperation between independent device and drug companies through a variety of means, including tax incentives, drug patent extensions, FDA-recognized patent terms for the new device, or a reduction of PDUFA/MDUFA fees or exclusivity for the combined use. These legislative remedies should be explored further. The CPC encourages a process to facilitate cooperation between these parties rather than attempt to find an FDA work-around in rulemaking. Further, new guidance from the Agency on premarket review standards for conventional cross-labeled products and their mutually conforming labeling would also help to encourage drug and device companies to collaborate in bringing new and innovative combination products to market.

II. Equity of Approval Pathways

FDA’s proposal would provide device and drug companies alike the opportunity to obtain a new drug claim through the PMA process. Although a PMA application is similar to a New Drug Application (“NDA”), as it requires sponsors to demonstrate safety and effectiveness through valid scientific evidence generally based on clinical trials, the approval standard for each application is different. New drugs require “substantial evidence [which] means evidence consisting of adequate and well-controlled investigations,”³ whereas new devices need only

³ 21 U.S.C. 355(d)(7).

demonstrate “reasonable assurance of the safety and effectiveness of the device.”⁴ An application by a device sponsor that would change the indication for a drug should require the same safety and effectiveness standards that would apply to a drug sponsor.

The CPC agrees with FDA’s first instruction set forth in the Federal Register Notice which requires DRD sponsors to provide substantial evidence of the safety and effectiveness of the new DRD label consistent with the standard that applies to new drug uses (21 U.S.C 355(c) and (d)). The CPC believes it is important that the evidence requirements for new drug uses are upheld in order to avoid inconsistent standards for drug reviews.

21 U.S.C. 355(b) requires that an NDA demonstrate substantial evidence by providing:

...(A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title.

In practice, most NDAs contain two or more well-controlled clinical studies in order to demonstrate substantial evidence. The evidence requirements are significant and have increased in complexity, which have also resulted in an increase in the time and cost of developing products. It is unclear how FDA will ensure consistent application of this standard in the PMA pathway.

In the absence of non-proprietary publicly available sources of information that meet these evidence requirements, it is unlikely that a device sponsor will have the resources to

⁴ 21 U.S.C. 360(a)(1)(C)(i).

demonstrate this level of evidence for a new drug use. Regardless, it is essential that FDA ensure there is no disparity in the evidence requirements that would apply to a drug sponsor submitting an application for a new drug use. In addition to the standard of evidence, the PMA and NDA pathways have different review timelines and user fee structures. Disparities in the level of evidence, timeline, or user fees required to make a new drug claim will steer sponsors toward the path of least resistance. This will have two unintended effects. First, the Agency runs the risk of approving new drug indications under a lower regulatory standard. Second, by accepting a different or lower bar to create a new drug claim, the Agency may inadvertently discourage cooperation between drug and device sponsors, as the device sponsor will have an easier pathway to receive regulatory approval.

If FDA demands the same level of evidence to support a new drug claim through the PMA pathway as is required under the conventional NDA pathway, which, as discussed above, is essential, it raises the question of why an NDA is not the most appropriate pathway for the approval *de novo*. A change in the intended use of a drug initiated by a medical device company likely raises drug-specific issues where the drug issues may predominate. Further, if the drug-device system under consideration is conventionally thought of as achieving a drug primary mode of action in a cross-labeled product, the product should continue to be classified as a drug with corresponding NDA and related drug requirements.⁵ The standard of approval should be based on the safety and effectiveness of the product, and not on the existence or non-existence of collaboration between sponsors.

III. Leveraging of Pharmaceutical Data by Device Companies

The DRD Federal Register notice posits that the DRD sponsor would be required to:

...provide all the information needed to evaluate the safety and effectiveness of the new use with the approved drug referenced in the DRD labeling, without relying on any proprietary information for the approved drug (e.g., by instead relying on non-product-specific published literature, generalizable knowledge).

⁵ Section 503(g) authorizes FDA to assign jurisdiction for combination products based on the product's primary mode of action ("PMOA").

The DRD sponsor may also be able to include in its application safety and effectiveness data and information from the marketing application for the drug that are publicly available, for example, if the approved reference listed drug has been withdrawn from sale, provided that FDA has determined that the approved reference listed drug was not withdrawn from sale for reasons of safety or effectiveness....

The CPC supports the concept that DRD sponsors may not rely on any proprietary information for the approved drug to obtain approval of the DRD PMA. However, the phrase “generalizable knowledge” is not clear in this context, and should be further defined prior to implementation of a DRD pathway.

Moreover, it is not clear if FDA is proposing that DRD sponsors could rely on previous FDA findings that the referenced drug product is safe and effective, and provide only the incremental data required due to the new intended use (indication, route of administration, dosing regimen, etc.) of the drug.

The CPC further recognizes that FDA has occasionally applied reduced data requirements using a truncated development pathway for premarket approval in the absence of statutory authorization when the agency concluded it was in the interest of the public health. The “paper NDA” policy⁶ and abbreviated new drug applications for drugs identical to DESI (Drug Efficacy Study Implementation) drugs⁷ are two examples.

On the other hand, other “abbreviated” regulatory pathways are founded on clear statutory authorization. Generic versions of drug products approved after 1962, through the Hatch–Waxman amendments to the Act are a clear example. The Hatch–Waxman amendments authorized FDA to approve 505(b)(2) new drug applications, which codified FDA’s paper NDA policy, and went further by permitting applicants to rely on “investigations that were not

⁶ See 45 Fed. Reg. 82052 (Dec. 12, 1980).

⁷ See Appendix to “Guidance for FDA Staff and Industry Marketed Unapproved Drugs – Compliance Policy Guide - Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs; September 2011; see also 43 Fed. Reg. 39126 (Sept. 1, 1978).

conducted by or for the applicant, and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.”⁸ For many years, FDA refused to extend 505(b)(2) provisions of the Food Drug and Cosmetic Act to biologics license applications (BLAs) licensed under the Section 351 of the Public Health Service Act. FDA did not begin to accept “abbreviated” BLAs until specifically authorized to do so in 2010 in the Biologics Price Competition and Innovation Act.

Finally, the 21st Century Cures Act implements a new version of Section 503(g)(3) of the Act, which states:

For purposes of conducting the premarket review of a combination product that contains an approved constituent part described in paragraph (4), *the Secretary may require that the sponsor of such combination product submit to the Secretary only data or information that the Secretary determines is necessary to meet the standard for clearance or approval, as applicable, under this Act or the Public Health Service Act, including any incremental risks and benefits posed by such combination product, using a risk-based approach and taking into account any prior finding of safety and effectiveness or substantial equivalence for the approved constituent part relied upon by the applicant in accordance with paragraph (5).*⁹

The CPC recognizes that DRDs and the referenced drug product do not fit the legal definition of a combination product, and so this provision is not directly applicable. We highlight this very recent statutory provision to demonstrate that most of the time, abbreviated regulatory pathways have a statutory foundation.

The CPC is not clear on what statutory foundation the proposed devices referencing drug proposal is based. The CPC recommends that FDA not develop the DRD pathway in the absence of statutory authorization. Among other things, statutory authorization would help

⁸ 21 U.S.C. 355(b)(2).

⁹ 21st Century Cures Act, Pub L. No. 114 – 255, <https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf> (2016)(emphasis added).

clarify what information the DRD sponsor could rely on and reduce confusion on the part of industry and FDA. Statutory authorization would eliminate all questions about FDA authority to implement the pathway and would help clarify the many thorny issues that bedevil the proposed pathway.

IV. Regulatory Status of the Drug After DRD Approval

The DRD Federal Register notice posits that the DRD applicant would be required to provide substantial evidence that the drug will have the effect it is represented to have in the proposed DRD labeling, and is safe for use under the conditions prescribed, recommended or suggested in the proposed DRD label. On the assumption that the DRD applicant provides the necessary data and information, and the DRD PMA is approved, it is not clear what FDA approval of the DRD PMA would mean for the drug product.

The Act permits any person to submit to FDA an application for “premarket approval for a class III device.”¹⁰ A drug will not likely meet the definition of a device,¹¹ Therefore, it is not clear whether approval of a DRD PMA could legally encompass FDA approval of the drug for use with the DRD device.¹² If the drug is not approved for use with the DRD device through approval of the DRD PMA, then what has FDA done with respect to the drug product? Failure to clarify this issue prior to implementation of a DRD pathway would surely result in significant confusion in industry and FDA, and require the expenditure of significant resources to resolve. In particular, failure to clarify this issue could lead to a manufacturer of an approved DRD device inadvertently misbranding its product by representing that the drug has been approved for use with the DRD device.

¹⁰ 21 U.S.C. §360e(c).

¹¹ It is likely that a drug product achieves its primary intended purpose through chemical or metabolic action, and therefore does not meet the definition of a device. See Section 201(g) of the Act, 21 U.S.C. §321(g).

¹² A similar situation may arise for drug-device combination products with a device primary mode of action that are reviewed under a device marketing application. However, FDA has recognized that combination products have unique characteristics that are different from stand-alone drugs, devices and biological products. These unique characteristics may permit the review and approval of drug constituent parts of combination products under a PMA.

Even if it is determined that the drug product is approved for use with the DRD device through approval of the DRD PMA, significant questions remain. Could the drug manufacturer promote its drug for use with the DRD device? Upon approval of the DRD PMA, could the drug manufacturer submit a supplement to the NDA or ANDA covering the drug to permit the drug to be labeled for use with the DRD device, and simply reference the DRD PMA? If the DRD PMA refers to a specific drug, would FDA approve generic versions of the drug labeled for use with the DRD device? If a patent is issued covering the use of the drug with the DRD device, could the drug manufacturer list the patent in the Orange Book? What would listing of the DRD patent mean for another device manufacturer who wants to develop a DRD for the same use, with the same drug or a different manufacturer's version of the same active moiety?

These are reasonably foreseeable questions arising from the approval of a DRD PMA, even if the DRD sponsor provides all necessary data and information about the drug product. Prior to implementing the DRD pathway, FDA should clarify the implications for the drug product of approval of a DRD PMA.

The FDA has already developed a draft guidance with respect to social media and mobile apps that parallels DRD issues. In its guidance FDA points out that third party developed content can be incorrect, misleading or recommend unsafe or unstudied use of branded drugs with significant risk to the public. As with DRDs, drug companies have few effective remedies when this occurs but would likely take some action on its own to protect patients.¹³

V. Drugs Referencing Devices

Although the CPC has identified a number of concerns with FDA's proposal, if FDA proceeds in making the DRD pathway available to device companies, a parallel approach should similarly be applied for drug sponsors. Similar to device sponsors, drug sponsors may also seek to obtain marketing authorization on new combined uses of a product where collaboration with a device company is not timely or feasible. Under a "drugs referencing devices" approach, the

¹³ FDA Draft: Guidance for Industry: Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices (2014), <https://www.fda.gov/downloads/drugs/guidances/ucm401079.pdf>.

safety and effectiveness of the combined use of the separately supplied device and drug could be demonstrated under the appropriate drug or biologic marketing pathway.

The drug sponsor would similarly need to satisfy the factors identified in the Federal Register Notice, but instead as they relate to the new use of the separately supplied device:

- demonstrate safety and effectiveness;
- address user confusion and medication error;
- address postmarket changes to the approved, marketed device;
- demonstrate a postmarket safety plan to address adverse events; and
- provide all information needed to demonstrate safety and effectiveness without relying on proprietary information for the approved device.

If FDA moves forward with the planned devices referencing drugs proposal, the Agency should describe a pathway through which a drug company could create a new intended use for a medical device without a corresponding update to the medical device product labeling.

VI. Summary

The CPC applauds the Agency's efforts to re-examine the challenges faced by the medical products industry related to products that are not able to achieve regulatory approval as cross-labeled combination products due to a lack of cooperation between the manufacturers of separately supplied drug or medical device products. The CPC has examined FDA's proposal on DRDs and believes that the current proposal of using the medical device PMA pathway to approve new drug claims raises a number of outstanding questions, including, but not limited to, the statutory authorities FDA considers to support the proposal; the ability for device companies and FDA to leverage prior conclusions of safety and effectiveness for the drug; and the regulatory status of the new drug indication after DRD PMA approval. The CPC recommends

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that the Agency clarify these and other elements of their proposal before implementing the DRD pathway, and provide appropriate opportunity for public comment.

Yours truly,

A handwritten signature in black ink, appearing to read "Bradley Merrill Thompson". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Bradley Merrill Thompson
On Behalf of the Combination Products Coalition