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Client Alert

FDA & Life Sciences Practice Group

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FDA Considers Approval Pathway for Medical Devices to Unilaterally Cross-Reference Marketed Drug Products

Would Not Require Collaboration by the Drug Sponsor; FDA Requests Comments on Potential Approach

The Food and Drug Administration (FDA) requests comment on a potential approval pathway for "devices referencing drugs" (DRDs).[i] Comments may be submitted until January 15, 2018.

A DRD is a device that would be expressly labeled for use with an approved, marketed drug product *outside the scope of the approved drug labeling* (e.g., a device labeled for use in the localized injection of a drug product that has otherwise been approved only for intravenous administration, or the use of a device to deliver a drug to a new site or for a new indication). In this scenario, the drug and device product sponsors would *not* be collaborating, and the drug labeling would *not* be modified.

FDA has proposed that a DRD sponsor could submit a premarket approval (PMA) application to the Center for Devices and Radiological Health (CDRH) containing the following information:

1. "Substantial evidence" of safety and effectiveness of the use;
2. Adequate directions for the DRD use;
3. A plan by the DRD sponsor to monitor changes to the marketed drug, and to address changes that could impact safety or effectiveness of the DRD use; and
4. A plan for reporting adverse events from the DRD use.

Speakers at an FDA public hearing identified considerations including:[ii]

- FDA will need to delineate adverse event reporting responsibilities, since drug sponsors would not be involved in supporting a DRD application, but would still have reporting responsibilities (and reasonably may receive communications) concerning their marketed drug products.
- Assuming that the same standards for safety and effectiveness associated with a new drug application (NDA) would apply for a DRD PMA, other NDA provisions (such as exclusivity for a use) should be carried through to the approved device that satisfied the NDA standard.

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- Existing data about a device and the marketed drug should be leveraged in determining the data requirements for a DRD.
- The type of submission should be based on known risks, such that perhaps a De Novo or 510(k) pathway also should be available for DRDs.
- Patients and care providers could be confused by the differing indications for a referenced drug, once a DRD is approved.
- This pathway could discourage drug and device companies from collaborating in the development of cross-labeled products. Incentives for collaboration (e.g., tax relief) should also be considered.

Our observations concerning the proposed DRD pathway include:

- The approval standard that FDA proposes for a DRD submission is "substantial evidence" of safety and effectiveness (the approval standard in the Federal Food, Drug, and Cosmetic Act (FDCA) for a new drug); however, the FDCA approval standard for a PMA or a new, high risk device is "reasonable assurance" of safety and effectiveness. How will these be consistently and appropriately applied?
- How would FDA apply NDA drug exclusivities to avoid erosion by a PMA approval?
- Would FDA have legal authority to offer exclusivity related to a PMA-approved drug product use?
- A DRD sponsor would have additional postmarket responsibility to continually monitor for changes to the referenced, marketed drug, which may be a challenging burden.
- Assuming FDA places DRD PMAs within the current PMA user fee structure, a potential gain for the DRD sponsor appears to be the much lower FDA user fee of about $302,000 for a PMA as opposed to roughly $2.4 million for an NDA. At the same time, if a sponsor is a small business submitting its first approval application, it would miss out on the one-time small business NDA fee waiver, and instead be subjected to the approximately $78,000 PMA fee and all the associated PMA-related fees thereafter.
- Under the current PMA user fee structure, if FDA determines that it does not need input from an advisory panel on a PMA, the review time frame for the submission is likely 180 days; otherwise, the review time frame would likely be 320 days (similar to a NDA review timeframe of 10 months). How would the Center for Drug Evaluation and Research respond to a request for the shorter action time?
- Non-collaborating drug product sponsors may face regulatory challenges to understand and manage information received about their products. They could face unanticipated product liability claims despite having no role in a DRD use.
- The 21st Century Cures Act includes certain provisions intended to facilitate combination product approvals, while preserving drug patent and exclusivity rights. For example, under the 21st Century Cures Act, a PMA application for a combination product would have to include patent certifications or statements, as applicable, and the PMA sponsor would have to provide notice to the approved NDA holder and patent owner. DRDs do not meet the statutory definition for a "combination product" inasmuch as the device and drug are not combined into one entity, provided together in one package, or cross-labeled (both products labeled for the combined use). Hence, the requirements of the 21st Century Cures Act for combination products do not apply to DRDs, and the DRD sponsor in the current proposal would not need to notify the sponsor of intended labeling concerning a drug under patent protection.

FDA has requested comments on a number of topics concerning its proposed DRD pathway, including safety and effectiveness standards and demonstration, potential user confusion and medication errors, postmarket change management, postmarket safety management, and data reliance (e.g., the ability to rely on published data in support of a DRD approval).

The proposed approach raises a host of novel legal and practical questions. King & Spalding will continue to monitor FDA's policy, guidance, and regulations for this new pathway. Please contact us as we can help you consider the DRD proposal and prepare comments, or determine whether your product would be subjected to the combination product provisions of the 21st Century Cures Act.

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[i] September 26, 2017 Federal Register Notice, available at, https://www.federalregister.gov/documents/2017/09/26/2017-20521/devices-proposed-for-a-new-use-with-an-approved-marketed-drug-public-hearing-request-for-comments.

[ii] FDA held a public hearing on November 16, 2017. More information, including a webcast recording, is available at: https://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/default.htm.