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FDA proposes streamlining combination product regulations

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On May 15, 2018, the Food and Drug Administration (FDA) proposed amending its product classification rules for combination products, found in 21 CFR Part 3. Generally, the proposed rule purports to clarify language in the regulations to enhance consistency with the 21st Century Cures Act (the Cures Act) and other guidance that has been released since the regulations were last amended, and to reflect accurately agency and industry experience in addressing combination product designations. Additional changes are proposed to specific procedures applicable to combination products, including clarification of the scope of product jurisdiction regulations and streamlining of the product classification appeals process. While clarification and alignment of the applicable regulations, policies, and current practices is helpful, the proposed rule downplays some of the opportunities for innovative change in the regulation of combination products suggested by Congress in the Cures Act by stating in a footnote that revision of Part 3 is "not necessary" because the agency's existing practices are already substantially in compliance with the Cures Act.

Major proposed changes:

1. Elimination of a pathway for sponsors to request that FDA reconsider a product classification determination.

Calling the existing request for reconsideration process – which is a step that allows a sponsor to appeal immediately within the Office of Combination Products (OCP) any initial product designation made following a Request for Designation (RFD) – "confusing and inefficient," the FDA has proposed to "remove" this process codified at 21 CFR § 3.8(c) for sponsors to request that the product jurisdiction officer reconsider determinations made under Part 3. In support of this proposal, the FDA asserted that such reconsideration requests, which rely solely on the same record submitted and considered under the RFD, are unlikely to result in a new determination. Sponsors would still be able to challenge the FDA's product classification determinations under the appeal pathways in 21 CFR § 10.75. Accordingly, there would not appear to be an opportunity for reconsideration of a jurisdictional determination directly within OCP, and appeals would necessarily involve personnel in the Office of Special Medical Programs. It is critical to note, however, that elimination of the request for reconsideration process would have no impact on any sponsor's ability to submit a new RFD for any designated product based on new information obtained in the future that changes the base knowledge about how a product acts in or on the body and thus may impact the designation of the product.

2. Clarification that only product sponsors can request product clarifications.

This proposal would preclude the industry from seeking broader classification determinations for new product types.

3. Removal of Intercenter Agreements.

Since 1991, the FDA has relied on guidance documents known as "Intercenter Agreements" between the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH) to outline the agency's general approach to review of various categories of products. These agreements, which are not binding on the FDA, broadly describe the categories of products within the jurisdiction of each center and provide examples of the kinds of products within each category. They also describe the underlying rationale by which similar products, or products with characteristics that may fall within more than one of the product categories or centers, may be assigned to a center for review. In the proposed rule, the FDA cites its September 2006 review of these Intercenter Agreements, and its finding that these agreements had "limited" usefulness, as support for the proposal to remove § 3.5, which addresses the relationship between Part 3 and Intercenter Agreements on product assignment. The proposed rule notes that the FDA is still considering these agreements in light of other policy statements to determine whether they remain helpful in defining review roles within the agency.

Analysis:

This proposed rule is generally limited in scope. It simplifies the appeals process, limits designations to product sponsors, and states that the RFD process, not previous Intercenter Agreements, are the primary mechanism by which product jurisdiction is likely to be addressed (while also leaving some ambiguity about whether written guidance like these Intercenter Agreements may still have some utility). However, the proposed rule does not address some of the larger issues related to combination product classification rules, such as cross labeling, nor does it address the Cures Act provision on "primary mode of action," which we discussed here. Indeed, in the proposal, the FDA gives only marginal recognition to the Cures Act, stopping short of addressing both structural and procedural issues that have long-existed with the RFD process. For example:

- The proposal retains the 15-page RFD limit, which allows little space to fully address OCP raised questions arising from theory, conjecture, or dated literature to prove the absence of chemical action contributing to a therapeutic effect. Lack of full discussion relating to such data and arguments can make it difficult to justify designation of a combination product and many single entity products with multiple effects as a medical device.

- The FDA's position has historically been that a component or product that exhibits any drug activity that contributes to its therapeutic effect could not be a medical device; yet, the Cures Act states that a drug/biological primary mode of action determination "cannot be based solely upon the product having any chemical action." The proposal fails to reconcile this apparent discrepancy.

It remains to be seen how the FDA will implement other provisions in the Cures Act specific to combination products such as the process for meetings with the OCP subsequent to a designation to discuss the type of data that will support the ultimate clearance or approval of the product. The

FDA's Cures Act deliverables tracker notes that additional guidance will be coming by December 2020.

This proposed rule follows other recent changes to FDA's practices on the classification and review of combination products. These other recent changes have primarily been issued through guidance documents, and the proposed rule does not officially codify any of these provisions:

- Guidance on how to prepare a pre-RFD submission
- Finalizing guidance on the classification of combination products
- Updating FDA forms and guidance documents to recommend declaration and discussion of combination products in meeting requests and marketing applications
- The proposal for a new regulations to distinguish Devices Referencing Drugs(DRDs) from combination products

The proposed rule is now open to comment from stakeholders, which are due to the FDA by July 16, 2018.

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