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A "cure" for combination products: 21st Century Cures Act mandates greater transparency of combination product designations

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The 21st Century Cures Act, signed into law on December 13, 2016, ushers in significant, and interesting, changes to the regulatory review of drug/biologic/device combination products. The regulation of combination products has been somewhat unpredictable and muddled over the last few years, leading many to complain that the current system poses a substantial barrier to innovation. While the Cures Act represents only a partial patch to the existing system, several provisions of the new law seek to bring consistency and efficiency to this complex area of regulation.

Primary mode of action determination and primary agency center assignment

One of the most controversial areas of combination product regulation over the past several years has been the determination of a product's "primary mode of action" (PMOA), which in turn determines the Food and Drug Administration (FDA) center that will have primary oversight for a specific product, as well as the path to market that the product must take. Many perceive FDA as often focusing on minimal or theoretical levels of "chemical action" in a proposed combination product as the basis to require regulation as a drug, even when regulation as a device may provide a less burdensome but sufficient level of oversight. The new law brings forth two important clarifications for this process.

Initial determination of PMOA

While the Cures Act codifies the current FDA practice of requesting a determination from the agency's Office of Combination Products (OCP) whenever jurisdiction is unclear, as well as maintaining the requirement for FDA to review a combination product under a single application "whenever appropriate," the Cures Act also clarifies the way in which FDA is to consider PMOA. This controversy was the central issue in the recent *Prevor v. FDA* litigation. Many in industry have criticized FDA for designating a combination product as having a drug PMOA when it has any chemical action. Because a "medical device" cannot "achieve its primary intended purposes through chemical action within or on the body...," FDA has been applying that standard to mean that any chemical action of the product made it fall outside the device definition, and that therefore it should be regulated as a drug.

The new provision in the Cures Act is worded narrowly and only prohibits FDA from "solely" basing the determination on chemical action without setting any other rules or standards for PMOA determination. Even so, the Cures Act requires FDA to determine PMOA as "the single mode of action . . . expected to make the greatest contribution to the overall intended therapeutic effects." Notably, FDA stated in a 2011 draft guidance document that its current position is that "the determination of whether a product meets the device definition does not depend solely on whether the product exhibits 'chemical action.'" Nonetheless, many in industry believed FDA had been acting otherwise. The Cures Act now clarifies how FDA is to interpret the device definition.

The Cures Act also provides for combination product meetings with FDA upon request after FDA makes its PMOA determination, during which the sponsor and FDA can discuss and agree upon issues and requirements that should be addressed by sponsor for approval of the product. This includes a process for agreeing on what are essentially "mechanism of action" studies that would allow a sponsor to demonstrate whether a product is likely to rely on a device, biologic, or drug mode of action. A significant question remains as to whether sponsors would be willing to invest in such studies solely to establish a regulatory pathway for an early stage product.

New PMOA determination appeal process

The Cures Act also creates a clear process for sponsors to challenge FDA's initial PMOA determination and agency center assignment under a mini-burden-shifting framework. It is not clear, however, precisely what problem the new provision seeks to solve. Most sponsors are able to interact quite closely with the agency's Office of Combination Products under the existing system. The overriding issue for most sponsors in this space has been the crafting of the ultimate regulatory path, and not the need for more interaction or process during the jurisdictional phase.

That said, under the Cures Act, if a sponsor disagrees with FDA's determination, the sponsor may now – as a matter of statute – request FDA's substantive rationale for its decision. FDA must supply the rationale and all scientific evidence FDA relied upon in making its PMOA determination. This change may be beneficial in some cases, where FDA has been less than clear about the evidence it relied on in making a determination, such as with Tissue Reference Group (TRG) advisory opinions regarding Section 361 human tissue and cellular products (where FDA has almost uniformly chosen not to provide feedback or insight into the basis for TRG opinions). Most OCP determinations under the request for designation process, however, do include an agency explanation. Rather, these determinations often cite literature or even patent filings that may suggest or leave open a question of whether the product may depend on chemical action. In cases like this, it is not the lack of an explanation – but the explanation itself – that leads to controversy.

Next, if the sponsor still disagrees, they may propose studies to establish the relevance of any chemical action in achieving the product's PMOA. The sponsor and FDA must collaborate and attempt to agree, within 90 calendar days of the sponsor's proposal, on the design of the proposed studies. Finally, if the sponsor and FDA agree on chemical action studies, the sponsor can conduct the agreed-upon studies and FDA must consider the resulting data and reevaluate its PMOA determination. FDA may then issue a new determination or leave its original determination intact.

Specifically offering the opportunity to conduct such studies may, ultimately, notably limit the viability of the appeal option. It is unclear how many sponsors would wish to conduct such studies. At the same time, although this process will lead to additional delays in product development and

of the review process (as well as add additional expense), the potential chance to change the primary review center responsible for reviewing the application may be worthwhile in some cases. This appeal process also appears to be Congress's response to the lengthy *Prevor v. FDA* litigation over the agency's designation of Prevor's combination product. In particular, the Cures Act appeal process is similar to the process undertaken by Prevor in attempting to change FDA's PMOA determination (minus judicial intervention).

Combination products with an approved constituent part

Another interesting change to the review framework for combination products is for those combinations that include an approved constituent part, such as an already approved drug to be used with a new device, or a cleared/approved device to be used with a new drug. Notably, the Cures Act's definition of "constituent part" does not include biological products licensed under the Public Health Service Act.

Although sponsors may freely decide to submit separate applications for constituent parts of a combination product, the Cures Act states that FDA may require a single application for the product if deemed to be necessary. In reviewing combination products with an approved constituent part, FDA may allow a sponsor to only submit information about the non-approved part(s) of the combination product, such as only requiring incremental risk and benefit data showing changes from the already-approved constituent part. This change may be critical in obtaining approval of a combination that incorporates constituent parts from two different sponsors. Often, it is extremely challenging, for example, for a device company using an approved drug to collaborate with the drug sponsor to provide FDA the necessary information or to change the drug's labeling.

Device application involving approved constituent drug

Notably, under the Cures Act, if an application is submitted as a new device for review under the Premarket Approval (PMA) or 510(k) processes and involves an approved drug component, the Cures Act essentially treats the application as a section 505(b)(2) new drug application for Hatch-Waxman purposes. In other words, the Cures Act requires that the device application include a Hatch-Waxman patent certification. The sponsor must also comply with Hatch-Waxman notice requirements as if the sponsor was submitting an NDA that references data or investigations not conducted by the sponsor and for which the sponsor does not have a right of reference.

Importantly, a combination product application that is submitted as a PMA or 510(k) application with an approved drug constituent part is also treated as a section 505(b)(2) application for new chemical entity, pediatric, qualified infectious disease, and orphan drug exclusivity purposes. However, such an application will now be subject to patent infringement statutes as if it were a section 505(b)(2) drug as well.

Combination product guidance

Further, the Cures Act requires that by December 2020, FDA issue – after a public comment period of at least 60 calendar days – a final guidance describing: the structured process for managing combination product pre-submission interactions; FDA's best practices for providing feedback

during pre-submission interactions; and information that must be submitted with a meeting request for a combination product. FDA must report statistics regarding the use of the PMOA determination appeal process to Congress as part of its annual combination products report.

Allowing specific deviations from cGMP

Last, although FDA has tried to address good manufacturing practice (GMP) for combination products via guidance and regulation (including finalizing, in January 2017, a guidance document entitled "Current Good Manufacturing Practice Requirements for Combination Products" (see our client alert on the guidance document), the Final Rule on Current Good Manufacturing Practice Requirements for Combination Products published in January 2013, and 21 CFR Part 4), under the new Cures Act provisions, FDA is required to publicly identify types of combination products and manufacturing processes that may adopt GMPs that differ from those required by existing regulations. FDA currently has in place a streamlined process by which sponsors are to comply with both applicable provisions of the drug current GMP (cGMP) and the device quality system regulation (QSR), for a drug and device combination made in the same facility. Under the existing process, FDA essentially deems most of those regulations equivalent, except for a few provisions from each set that would still be required to augment the base system. This new statutory change may streamline the process even further. In order to meet the statutory requirements, FDA must publish a proposed list in the Federal Register by June 2017, hold a public comment period, and issue a final list of applicable GMPs in the Federal Register.

Contacts

Robert Church
Partner, Los Angeles
Tel +1 310 785 4646
robert.church@hoganlovells.com

David Fox
Partner, Washington, D.C.
Tel +1 202 637 5678
david.fox@hoganlovells.com

Heidi Gertner
Partner, Washington, D.C.
Tel +1 202 637 5676
heidi.gertner@hoganlovells.com

Yarmela Pavlovic
Partner, San Francisco
Tel +1 415 374 2336
yarmela.pavlovic@hoganlovells.com

Randy Prebula
Partner, Washington, D.C.
Tel +1 202 637 6548
randy.prebula@hoganlovells.com

Jodi Scott
Partner, Denver
Tel +1 303 454 2463
jodi.scott@hoganlovells.com

Justin Yu
Associate, Los Angeles
Tel +1 310 785 4642
justin.yu@hoganlovells.com