REGULATORY FOCUS

Amendments to the 21st Century Cures Act: Changing the Regulation of Combination Products

By Robert D. Cumming and Nancy W. Mathewson, Esq

This article summarizes regulatory changes impacting how premarket applications for combination products will be reviewed by FDA and procedures and reporting requirements for applicants and FDA as required by the 21st Century Cures Act.

Introduction

Combination product premarket notifications (510(k)), Premarket Applications (PMA) and Requests For Designation (RFD) to the US Food and Drug Administration (FDA) have increased substantially over the last decade with the number of regulatory submissions for this type of regulated product increasing annually.{1} Section 3038 of the *21st Century Cures Act* (13 December 2016), *Combination Product Innovation*, amends exemptions and consideration for certain drugs, devices and biological products of the Federal Food Drug and Cosmetic Act (FDCA) by the addition of regulations within subsection 353(g), *Regulation of Combination Products*.{2,3} The regulatory amendments codify procedures previously only recommended in guidance documents.{4,5} Compliance with these procedures for resolving classification disputes over Primary Mode of Action (PMOA) of a combination product or a disagreement specific to interpretation of information requested by FDA to support a marketing application is now required by the applicant and FDA. In addition, regulatory review timelines for FDA and reporting requirements to Congress by FDA have been codified.

Mode of Action, Primary Mode of Action and FDA Center Jurisdiction

Each component of a combination product has an identifiable Mode of Action (MOA). The MOA is the means by which a product achieves an intended therapeutic action or effect or action (*21 CFR 3.2(k)*).{6} The device, drug or biologic component having the MOA

Table 1. Marketed Combination Products, PMOA and Lead Center

Combination Product	Therapeutic PMOA	Lead Center
Drug coated coronary stent	Device – structural/not metabolized	CDRH
Dental sealant with antibiotic	Device – structural/not metabolized	
Dialysate with drug component	Device – functional/not metabolized	
Joint prosthesis coated with growth factor	Device – functional/not metabolized	
Drug with injector device	Drug – chemical action/metabolized	CBER
Radiopharmaceutical with carrier device	Drug – chemical action/metabolized	
Drug and activating light source	Drug – chemical action/metabolized	
Insulin and inhaler device	Drug – chemical action/metabolized	
Stem cells and implantable delivery device	Biologic – chemical action/metabolized	CBER
Tumor derived antigens for diagnostic use	Biologic – chemical action/metabolized	
Interferon and injector for treatment of hepatitis C	Biologic – chemical action/metabolized	
Gene therapy and drug for treatment of malignant glioma	Biologic – chemical action/metabolized	

expected to make the greatest or primary contribution to the overall intended therapeutic effect of the combination product determines the appropriate lead center for the product's regulatory oversight. Which FDA agency with primary jurisdiction over the combination product—the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER)—is determined by the product's PMOA. The Office of Combination Products (OCP), established in 2002 under the *Medical Device User Fee and Modernization Act*, is responsible for assigning an FDA center with primary jurisdiction for the review and post-market oversight of a combination product.{7} Once a lead center has been assigned, that center may consult any other center(s) during the regulatory review. Examples of combination products, their PMOA and the lead center responsible for regulatory and all other oversight are presented in **Table 1**. Amendments within the *21st Cures Act* do not change these definitions nor do they change how a lead center is assigned jurisdictional authority.

Combination Product Regulatory Amendments within the 21st Century Cures Act

Section 3038 of the 21st *Century Cures Act* amends Title 21—Food and Drugs, Chapter 9—Federal Food, Drug, and Cosmetic Act, Subchapter V—Drugs and Devices, Part A—Drugs and Devices, Section 353(g)—Regulation of Combination Products. The codified amendments will put into effect mandatory regulations affecting how combination products are regulated by FDA and procedures for applicants when there is a need for clarification of either a product's PMOA or the requirements indicated by FDA as to how a product should be classified or regulated. The context of some, but not all, of the new regulations may be found in existing guidance documents as nonbinding recommendations. The additional regulations of interest to applicants are summarized below.

1. A combination product premarket notification or marketing application is to be submitted to only one center. Whenever appropriate, premarket review of any combination product is to be conducted under a single application and one set of regulations.
2. A combination product that includes a device and a drug or a biologic is not necessarily regulated as a drug or biologic product. The PMOA of a combination product is not determined to be that of a drug or biological product solely because the product has a chemical or biological action within or on the body.
3. FDA will explain the rationale behind any agency decision/recommendation and collaboratively work with the applicant to resolve issues related to the PMOA determination or information required by FDA for the application to proceed through the review process. In the event of disagreement by an applicant over a PMOA determination, the secretary of the Health and Human Services is to: provide the rationale and scientific evidence to support the determination; allow

the applicant to propose a study to establish chemical or physical action as the PMOA; collaborate and reach agreement within 90 days on the study design; and consider the resulting study data when re-evaluating the determination of the PMOA.

4. The applicant of a combination product is allowed to request a meeting with FDA to obtain a preliminary and nonbinding assessment of the regulatory classification of the product and the identification of the center that would have jurisdiction over the product life cycle (a "pre-RFD meeting"). If the secretary concludes a meeting is necessary, he/she is to meet with the applicant within 75 days of receiving a meeting request from the applicant.
5. On agreement by the secretary that a pre-RFD meeting is appropriate, at the conclusion of that meeting, the applicant and secretary are to reach agreement in writing as to: standards and requirements for market approval or clearance; applicable requirements related to good manufacturing practices and any post-market modifications; and any scientific or other information required at a later date. The written agreement is to remain in effect except upon written agreement by the secretary and the applicant.
6. Applicants for a combination product that includes both a marketed product and an investigational product are only required to submit data to support the safety, effectiveness or performance of the unapproved constituent part. The applicant may submit only data or information as determined by the secretary to be necessary for meeting the standards for clearance or approval of the unapproved product, including any increased risks or benefits posed by the combination product, taking into account safety and effectiveness for the approved constituent part.
7. Evidence is required to demonstrate a patent infringement does not occur for a combination product that includes an approved drug. An application submitted for approval of a combination product having a device PMOA with an "approved drug" constituent part must include certification by the applicant showing that either the drug patent information has not been filed, the patent has expired or the date on which the patent *will* expire, or that the patent is invalid or will not be infringed by the manufacture, use or sale of the combination product.
8. In addition to identifying a lead center, the OCP designates a person or persons in the jurisdictional center as the primary point(s) of contact for the combination product applicant. That person coordinates communications between consulting centers involved in the premarket review if requested by the primary review center or any consulting center. Additionally, the OCP is to: ensure any meeting between the secretary and the applicant is attended by at least one representative from each agency center involved in the premarket review, as appropriate and require each consulting center to complete its premarket review and, in a timely manner, submit the results to the primary center.
9. Within four years from the date of enactment, the secretary is to issue a final guidance based on the experience gained during those four years that describes: the structured process for managing pre-submission interactions with applicants developing a combination product; best practices for ensuring timely and constructive feedback to applicants; and the information required within a pre-submission meeting request.

Conclusion

Prior to the *21st Century Cures Act* and the *Combination Product Innovation Amendment*, FDCA did not include regulations for pre-submission meetings with FDA or for the adjudication of disagreement as to the PMOA between an applicant and any of the three reviewing centers or the OCP for combination products. Section 3038 of the *Cures Act* codifies procedures an applicant must follow to request a preliminary meeting with FDA. That section also extends regulations to include requirements, center priorities, review standards and timelines to ensure inter-center consistency in the premarket review of a product comprised of two or more unapproved constituent parts or for a product in which a device,

drug or biologic constituent part is a regulated product (i.e., cleared or approved) and the other(s) is not.

The *21st Century Cures Act* amendments to the FDCA call for a single premarket review of any combination product, whenever appropriate, and clarify that because a combination product may have a chemical action within or on the human body, the product does not necessarily have a drug or biological PMOA. Furthermore, the OCP is to assign a designated person in the primary agency center as the applicant's point of contact. The amendments also explain options an applicant may exercise if there is disagreement in the determination of the PMOA. Regulatory submission and reporting requirements by the applicant to FDA and FDA's release of guidance documents and reports to Congress also are mandated through the additional regulations.

References

1. Combination Product Review. Intercenter Consult Process Study. Department of Health and Human Services. October 2015. http://www.fda.gov/downloads/combinationproducts/guidanceregulatoryinformation/ucm467128.pdf. Accessed 10 April 2017.
2. *The 21st Century Cures Act* (Division A of P.L. 114-255). Congressional Research Service. December 23, 2016. https://fas.org/sgp/crs/misc/R44720.pdf. Accessed 10 April 2017.
3. *Federal Food, Drug and Cosmetic Act.* 21 US Code 353. Exemptions and Consideration for Certain Drugs, Devices, and Biological Products. https://www.law.cornell.edu/uscode/text/21/353. Accessed 10 April 2017.
4. *Classification of Products as Drugs and Devices and Additional Product Classification Issues. Draft Guidance for Industry and FDA Staff*. June 2011. https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM258957.pdf. Accessed 10 April 2017.
5. *Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product. Guidance for Industry and FDA Staff*. May 2004. https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147126.pdf. Accessed 10 April 2017.
6. 21 CFR 3.2 (k). Definitions. https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=2ce0b0072efee1df1a01f2d520df371a&ty=HTML&h=L&mc=true&n=pt21.1.3&r=PART#se21.1.3_12. Accessed 10 April 2017.
7. *Medical Device User Fee and Modernization Act of 2002.* https://www.fda.gov/downloads/ForIndustry/UserFees/MedicalDeviceUserFee/ucm109135.pdf. Accessed 10 April 2017.

About the Authors

Robert D. Cumming is the regulatory manager within the medical devices and diagnostics group at PPD and has more 30 years of experience in high-risk medical device research and development, preclinical and clinical evaluations, and regulatory affairs. He can be contacted at Robert.Cumming@ppdi.com.

Nancy W. Mathewson, Esq, is the director of regulatory affairs for the medical devices and diagnostics group at PPD and has more than 30 years of experience in the medical device and pharmaceutical industries. She can be contacted at Nancy.Mathewson@ppdi.com.

Cite as: Cumming, R.D. and Mathewson, N.W. "Amendments to the 21st Century Cures Act: Changing the Regulation of Combination Products." *Regulatory Focus*. April 2017. Regulatory Affairs Professionals Society.