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Locke Lord QuickStudy: New Rules for Drug-Device Combos

Locke Lord LLP

FDA recently issued its new final guidance concerning the appropriate pathway for review of drug-device combination products, *Principles of Premarket Pathways for Combination Products Guidance for Industry and FDA Staff*. In this new guidance document, FDA sets forth a description of the process by which applications seeking approval of combination products including a drug and device, a drug and biologic, or a biologic and device will be reviewed.

Lead Center and the Primary Mode of Action

In the guidance, FDA notes that each combination product will be assigned to one of three specific divisions: Center for Drug Evaluation and Research ("CDER"), Center for Biologic Evaluation and Research ("CBER"), and Center for Devices and Radiological Health ("CDRH") to lead the product's review. FDA will select the lead center based on its understanding of which constituent part of the combination will be responsible for its primary mode of action ("PMOA"). For example, in dealing with a combination product consisting of a biologic product that and an auto-injector, FDA would refer the product to CBER based on the primary efficacy of the product being attributable to the biologic. A combination product consisting of a stent coated with an anticoagulant drug, however, would be assigned to CDRH based on the primary efficacy of the product being attributable to the stent.

After a combination product gets assigned to a lead center, that division will coordinate the review of the regulatory application, including the involvement of other centers as necessary. If an applicant disagrees with the lead center assignment or the PMOA assessment, an applicant may submit a request for designation ("RFD") identifying which division the applicant views would be most appropriate to lead regulatory review, including justification for why the FDA's PMOA assessment is inaccurate.

Submitting a Combination Product Application

The guidance also includes instructions for applicants regarding the selection of the appropriate type of application for combinations products in accordance of with the requirement in Section 503 of the Federal Food, Drug, and Cosmetic Act that FDA "shall conduct the premarket review of any combination product under a single application, whenever appropriate." Under the guidance, the application filed should generally coincide with the PMOA. Device-led combination products should be filed as a PMA or 510(k) application. Drug-led combination products should be filed as a NDA or ANDA. Biologic-led applications should be filed as a BLA or 351(k) application.

FDA also notes in the guidance that even though each combination product should be filed under only one application category, the application should include all of the sections necessary to evaluate the combination product as a whole. In determining which sections are necessary for each combination product application, FDA refers applicants to the individual guidance's it has issued on the structure and content of individual drug, biologic,

and device applications. For example, a NDA on a new chemical entity administered with an inhaler should include not only all of the sections necessary to review the new drug for safety and efficacy but also the sections that would be required as part of a PMA or 510(k) to ensure safety and efficacy of the inhaler device. CDER would then assign out the inhaler sections to personnel at CDRH to review the device in parallel to its review of the new drug for approvability. A chart outlining the appropriate application for various combination products is presented below:

Product	PMOA	Application	Additional Sections
Generic drug in pre-filled syringe	Drug	ANDA	510(k) for syringe
Artificial eye lens with generic antibiotic coating	Device	PMA	ANDA for antibiotic
New biologic entity administered by topical patch	Biologic	BLA	510(k) for patch
Arterial stent with reservoir of generic anticoagulant	Device	510(k)	ANDA for anticoagulant
New chemical entity and follow-on biologic contained in solution for intravenous use	Drug	NDA	351(k) sections for follow-on biologic

Recommendations

Filing the incorrect type of application for a new combination product or failing to include necessary sections of an application likely will result in significant delays to both the review and approval process. Before committing to an application type, the regulatory team should undertake a thorough analysis of the product's PMOA and identify all of the relevant application sections necessary for inclusion to ensure FDA has all it needs to conduct its approval assessment as quickly as possible.

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