PHARMACEUTICAL ONLINE

Guest Column | October 4, 2019

Comparing New U.S. & EU Guidances On The Combination Product Approval Process

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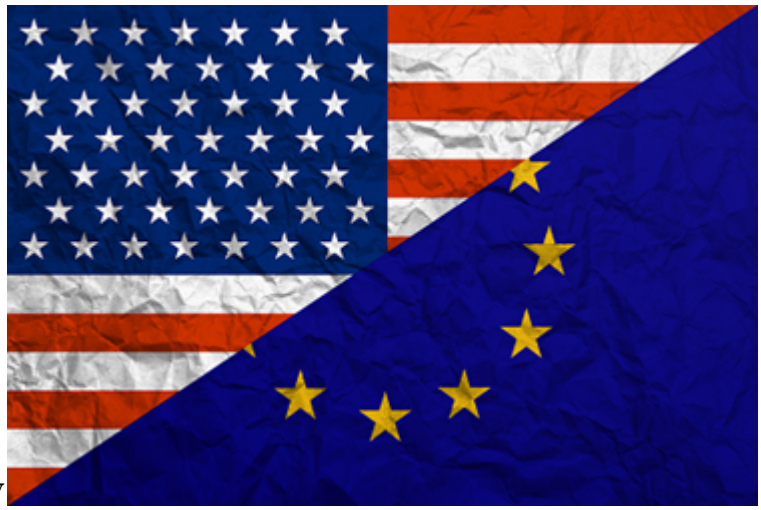

The rapid growth in combination products available in the global pharma and biotech marketplace has prompted both the FDA and the European Union to update their guidance on how such products are reviewed and approved for sale. The new EU draft guidance, *Guideline on the quality requirements for drug-device combinations,* and U.S. draft guidance, *Principles of Premarket Pathways for Combination Products,* are the latest attempts by each regulatory body to adequately regulate combination products. In Part 1 of this two-part series, we examined the U.S. regulatory guidance. In Part 2, we cover the European Union guidelines for combination products and show how the U.S. and the EU diverge.

Guideline On The Quality Requirements For Drug-Device Combinations (EU)

Regulation of combination products in the European Union is in its infancy. The EU does not have a category of product for combinations; it only addresses medical devices and medicinal products. However, in May 2017 the new Medical Device Regulation (MDR)[1] was released to supersede the previous Medical Devices Directive (MDD).[2] Unlike the MDD, the MDR included articles addressing devices designed and sold with a medicinal product as an integral part. These drug-device combinations are separated into two categories:

> Article 1(8) Devices incorporating as an integral part a substance that, if used separately, would be considered a medicinal product *and* the action of the substance is principal.
>
> Article 1(9) Devices intended to administer a medicinal product where they form a single integral product intended exclusively for use in the given combination which is not reusable.

In addition to defining the two categories, Article 117 went on to modify Directive 2001/83/EC[3] governing medicinal products for human use. The amendment stated that products governed by the directive that include a device part as defined by Article 1(8) and Article 1(9) shall include in the marketing authorization the results of the assessment of conformity of the device part with the relevant general safety and performance requirements from Annex I of the MDR included in the manufacturer's EU declaration of conformity, or in a certificate issued by a notified body. If the marketing authorization for the combination product does not include the conformity assessment, a notified body must be involved and issue an opinion on conformity of the device part with the MDR general safety and performance requirements.

In layman's terms, when a drug-device combination product manufacturer submits a marketing authorization application to the EMA, it must include an official certificate of conformity that the device complies with the MDR. In effect, each drug-device combination product will go through two assessments — one for the device and one for the product as a whole — before being put on the market.

How The EU And U.S. Diverge

This process is in direct contradiction to the process for combination product approval in the United States. The FDA has gone to great lengths to ensure that combination product manufacturers do not have to duplicate work, but the EU has just mandated a burdensome process of approval for each constituent part of drug-device combination products. The consequence is dramatic for any company wishing to put a combination product on the market in the EU. The length of time it will now take to get a product approved is likely doubled. This is compounded by the fact that the new MDR regulates notified bodies to such an extent that a significant portion of notified bodies are closing shop. Now that drug manufacturers are required to do the same, it is going to be an even bigger burden on an already burdened system.

Unsurprisingly, this change to the directive created a significant amount of confusion. EMA immediately began addressing the confusion by publishing a *Concept paper on developing a guideline on Quality requirements of medicinal products containing a device component for deliver or use of the medicinal product*. The concept paper describes the agency's thinking on why the new guideline was necessary. The EMA decided to draft this guideline based on the prevalence of marketing authorizations' dossiers for drug-device products submitted with data that was inconsistent and often incomplete. It also noted there has also been an increase in the number of applications to request scientific advice for drug-device combinations.

Additionally, EMA wanted to clarify that the notified body assessment and marketing authorization review would not result in duplicate assessments. While the notified body will review the device alone, EMA clarified that the marketing authorization review will assess the implications of drug-device product on the safety and efficacy of the drug product (which EMA is concerned may be compromised by the inclusion of the device part). This clarification of intent assures manufacturers

that device conformance with MDR Annex I will not be assessed twice. Nonetheless, the lack of duplication in reviewing the device does not mean that the product won't still have to go through two separate assessments.

The *Guideline on the quality requirements for drug-device combinations* comprehensively describes the process that drug-device product manufacturers will need to follow to submit a marketing authorization to the EMA. The Guideline goes into detail about the required contents of the marketing authorization dossier. The completeness of the Guideline provides manufacturers with answers about the logistics of review for new drug-device products. The Guideline is currently in draft form and industry may submit comments. However, the EMA does not publish comments during the review period. As a result, industry opinion is unclear. Ultimately, the Guideline does not appear controversial because it does not introduce unexpected requirements based on the MDR's modifications to the Directive. In fact, clarification on the process should be welcomed.

Implications For international Manufacturers

The process of putting a combination product on the market with a device constituent part is now more burdensome in both the United States and the EU. The United States is making it clear that just because a combination product has a device component does not mean it will get an easier review process. Restricting access to the 510(k) pathway is going to create a burden and may decrease enthusiasm for putting combination products on the market in the United States. With the added burden in the EU, combination products seem even less appealing. Now the two biggest markets in the world are going to require extensive work for approval. Combination products in the U.S. are going to need go through the PMA or NDA processes, which are much more expensive than the 510(k). This introduces the requirement for clinical trials and additional non-clinical and analytical testing. The EU will likely require the same for every drug-device combination product. On the bright side, manufacturers that go through the effort of getting a combination product approved in the United States through a PMA or NDA will be well positioned to put a product on the market in the EU. The amount of data developed should be sufficient to demonstrate conformance with Annex I of the MDR and, ultimately, put the product on the market in the EU through the EMA centralized procedure.

Patients And Combo Devices

For patients, the increased regulatory burden has pros and cons. The products that make it to the market will be thoroughly reviewed for safety and efficacy, and treatment outcomes should be better for patients, with fewer adverse effects and increased efficacy. However, new combination products will be much slower to arrive on the market, especially in the EU. This may be frustrating for patients because of the specific role the drug-device combination products have in medicine. The reason drug-device combinations are so appealing is that they decrease the burden of taking medication. Using products to release drugs at a regulated rate increases efficacy, because they make compliance with drug regimens simpler. The convenience is better for patients and better for manufacturers because it leads to more positive outcomes for patients. Additionally, these products

decrease adverse effects because they reduce the likelihood of overdosing or underdosing on a prescribed medication. Both patients and manufacturers will need to watch closely to see how the new regulations affect trends in the market. With any luck, there will be an opportunity for innovative combination product manufacturers to swoop in on a market that may have fewer participants due to the extra regulatory burdens.

Next Steps

First and foremost, combination device makers need to read the guidances and comment to both agencies. The FDA is legally required to address comments and consider whether they should result in changes to the guidance. The EMA will also consider implications of comments on the guideline and potentially make changes if enough parties identify gaps. Once the guidances are finalized, getting to know them in detail is essential. Both are going to shape the way applications for drug-device products go forward. Manufacturers in both the U.S. and EU should adjust their timelines for putting products on the market based on the new guidance. However, for drug-device products in the United States that have a very similar device predicate, there is an argument that a 510(k) application should be submitted with the non-combination product predicate, regardless of the new guidance. Individual reviewers make the final decision on whether a predicate is sufficient. However, it is essential that a manufacturer considering that path go through a presubmission meeting/WRO. It is not worth submitting a marketing application directly for a 510(k) and having it rejected as Not Substantially Equivalent because a company decided to roll the dice and select a non-combination product predicate device without seeking agency guidance.

Ultimately, the reality of the changes in the MDR and the adjustment in the FDA's expectations of drug-device product approval pathways are likely here to stay. It's going to be a difficult adjustment, but in the EU it is necessary. The MDR was written over years and has entirely changed the EU market. There is no chance that it will be modified to roll back this burden in the short term. In the United States, the FDA has been realizing for years that the 510(k) process is too easy for products that present new risks because of a combination of drug and device. This change was inevitable, because the FDA has been getting smarter about these products. The best plan for manufacturers with long-term plans for multiple drug-device combination products is to begin modifying your procedures, development processes, and testing plans now in preparation for meeting the new standards.

References:

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About The Author:

Caitlin Bancroft, JD, is passionate about facilitating advancements in healthcare quality and medical technology by ensuring compliance for medical device, pharmaceutical, and biologic product regulatory requirements. Her experience in medical device regulation spans Class III, 510(k), PMA, De Novo, Modification, Reclassification, and IDE. Her work includes the review of FDA and EU regulations concerning quality management systems, cGMPs, clinical evidence/trials, complaint handling, risk management, and registration requirements for product classification and regulatory compliance of medical device, pharmaceutical, biotech, and human tissue/cell products. She works closely with clinical, quality management, and product and process development teams to accomplish cGMP audits and write clinical evaluation reports on behalf of Pharmatech clients.