US Regulation of Combination Products

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Maria Donawa

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The successful launch of a combination product in the United States (US) will depend on how well a company understands applicable US regulations and policies, which differ in important ways from requirements in Europe. This article provides an overview of useful information on the US regulation of these products that can be found on the newly redesigned Food and Drug Administration website.

A comprehensive resource

Companies seeking to understand the United States (US) regulation of combination products should visit the Food and Drug Administration's (FDA) website, www.fda.gov/CombinationProducts/default.htm, which contains comprehensive information on the subject; of particular use are the links provided on

- Combination Product Definition
- Acts, Rules and Regulations
- Office of Combination Products
- Combination Products Guidance Documents
- Request for Designation Process
- Frequently Asked Questions About Combination Products
- Intercenter Agreements
- Jurisdictional Transfers
- Jurisdictional Updates
- Request for Designation (RFD) Jurisdictional Decisions
- Meetings, conferences and workshops.

The information in "Frequently Asked Questions About Combination Products" provides a useful introduction to those unfamiliar with the US approach to the regulation of these products. For example, the questions answered include: What is a combination product? What are some examples of combination products? What are the roles of the Office of Combination Products? How are combination products assigned for review?

In addition to the subjects listed above, there is a link to examples of specific combination products that have been approved by FDA. These include a transdermal patch to treat attention deficit hyperactivity disorder in children, the first inhaled insulin combination product for the treatment of diabetes, a device–biological product gel for surgical haemostasis, together with other examples. Unfortunately, no information is provided on how these products were cleared by FDA or which FDA centre took the lead.

Combination product definition

The term "combination product" is defined in the US 21 Code of Federal Regulations (CFR) 3.2(e), as

1. A product comprised of two or more regulated components, that is, drug/device, biologic/device, drug/biologic or drug/device/biologic, which are physically, chemically or otherwise combined or mixed and produced as a single entity.
2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products or biological and drug products.
3. A drug, device or biological product packaged separately that according to its investigational plan or proposed labelling is intended for use only with an approved individually specified drug, device or biological product, where both are required to achieve the intended use, →

Dr Maria E. Donawa

physician, pathologist and pharmacist with nearly 30 years' regulatory experience, worked with the US FDA before becoming President of what is now Donawa Lifescience Consulting, an international consultancy company, which provides regulatory, quality and European Authorised Representative services to life science companies and is a full service European CRO.

indication or effect, and where on approval of the proposed product the labelling of the approved product would need to be changed, for example, to reflect a change in intended use, dosage form, strength, route of administration or significant change in dose.

4. Any investigational drug, device or biological product packaged separately that according to its proposed labelling is for use only with another individually specified investigational drug, device or biological product where both are required to achieve the intended use, indication or effect.

There is no single definition in the European Directives for combination products. Instead, the regulation of products made up of drug, device or advanced therapy medicinal products are addressed in Article 1 (3), (4) and (4a) of the Active Implantable Medical Device Directive (90/385/EEC); in Article 1 (3), (4) and (4a) of the Medical Device Directive (93/42/EEC); and in the Advanced Therapy Medicinal Products Regulation (EC) No 1394/2007.

Acts, rules and regulations

Companies intending to market combination products in Europe and the US should recognise at the beginning of the project that although there are some similarities between the European and US regulations, there are also important differences. Links to 21 CFR Part 3 and other regulations regarding combination products, as well as to the definitions of biological product, drug and device, are found on the web page "Acts, Rules and Regulations," which can be accessed from the FDA's combination products home page under "Guidance & Regulatory Information" and "Resources for You."

Table I: The general OCP guidance documents listed on the "Combination Products Guidance Documents" web page.

- Technical Considerations for Pen, Jet and Related Injectors Intended for Use with Drugs and Biological Products (2009)
- New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products (Draft Guidance) (2008)
- Devices Used to Process Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps) (2007)
- Minimal Manipulation of Structural Tissue (Jurisdictional Update) (2006)
- Early Development Considerations for Innovative Combination Products (2006)
- How to Write a Request for Designation (RFD) (2005)
- Application User Fees for Combination Products (2005)
- Current Good Manufacturing Practice for Combination Products (Draft Guidance) (2004)
- Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product (2004)

The primary US regulation on combination products is in 21 CFR Part 3, Product Jurisdiction. This specifies how FDA will determine the "agency component" that will have primary jurisdiction for the premarket review and regulation of combination products. This regulation also provides procedures for determining which FDA component will have primary jurisdiction for any drug, device or biological product where this jurisdiction is unclear or in dispute.

The regulation that specifies how FDA designates the review of combination products, which is based on the Primary Mode of Action (PMOA) of a product, is in 21 CFR 3.4, Designated Agency Component. The agency component means the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), or alternative organisational component of the agency. The PMOA is the single mode of action of a combination product that provides the most important therapeutic action; this is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.

Office of Combination Products

The FDA Office of Combination Products (OCP), established on 24 December 2002, is an important resource for companies seeking to market combination products in the US. This is particularly the case when questions exist regarding the manner in which these products will be regulated in the US and for single products where the regulatory jurisdiction is unclear.

The OCP has broad responsibilities covering the regulatory life cycle of combination products. It is important that companies understand the role of the OCP, which includes

- serving as a focal point for combination product issues for FDA reviewers and industry
- developing guidance and regulations to clarify the regulation of combination products
- assigning an FDA centre to have primary jurisdiction for review of combination and single entity (noncombination) products where the jurisdiction is unclear or in dispute
- ensuring timely and effective premarket review of combination products by overseeing the timeliness and coordination of reviews involving more than one agency centre
- ensuring consistency and appropriateness of postmarket regulation of combination products
- resolving disputes regarding the timeliness of premarket review of combination products
- updating agreements, guidance documents or practices specific to the assignment of combination products
- submitting annual reports to Congress on OCP activities and impacts.

Guidance documents

Since the establishment of the OCP, several guidance documents have been developed, some of which are still in draft form. The list of general OCP guidance on product classification, jurisdiction and combination products can be found on the "Combination Products Guidance Documents" web page (see Table I). A link to this page is provided in several places on the FDA's combination products home page, including "Guidance & Regulatory Information" and it is the single item under "Key Topics."
In addition to these documents, OCP states that it is in the process of compiling a list of guidance documents developed by each of the FDA review centres involved in the assessment of combination products that OCP believes would be of interest to combination product sponsors. These centres are the CBER, CDER and CDRH; however, this list is not yet available.

Request for Designation process

Requests for assignment of a combination product to an FDA centre or a determination of the regulatory identity of a product as a drug, device, biological product or combination product may be managed in a formal or informal manner. A formal request is made through the Request for Designation (RFD) process. FDA will make its jurisdictional determination within 60 days of filing the RFD. It is advisable, however, to contact FDA in an informal manner before the submission of an RFD. This is because FDA may have enough experience with similar products to allow a determination to be made without the submission of an RFD.

If an RFD is considered necessary, it will be important to review the RFD process as it is described in 21 CFR 3.7 and to refer to the FDA guidance, "How to Write a Request for Designation (RFD)," which is found on the FDA's combination products home page under "Industry Resources."

Jurisdictional updates

In response to requests by interested parties that FDA should provide more information on the RFD process and related FDA decisions, FDA has posted a series of "jurisdictional updates" on its "Jurisdictional Update" web page, which can be found on the FDA's combination products home page under "Classification and Jurisdictional Information" or "Industry Resources." These updates cover the following products:

- breath test combination products
- dental prophylaxis pastes with drug components
- drug–device combination catheter lock/flush solutions
- drug-biologic combination products
- drug-eluting cardiovascular stents
- human demineralised bone matrix
- metered dose Inhalers, spacers and other accessories.

FDA states that jurisdictional updates report FDA decisions, but they are not FDA policy statements, which is an important point to note. They do provide useful insight into FDA thinking on jurisdictional issues at the time the decisions were made, however, new information developed subsequently may lead FDA to different jurisdictional decisions.

A valuable resource

European regulations make it relatively easy to understand which is the appropriate regulatory route to market for a product that includes elements that, if considered separately, would be either a medicinal product or a medical device. The US process for regulatory review and clearance is not so transparent. For this reason, prudent companies intending to market these types of products in the US should review the comprehensive information available on the FDA's combination products website to gain a better understanding of how their particular devices may be assessed and which review centre is likely to take the lead in the process. mdt

Maria E. Donawa
Donawa Lifescience Consulting, Piazza Albania 10, I-00153 Rome, Italy, tel. +39 06 578 2665, e-mail: medonawa@donawa.com
www.donawa.com

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