Current US Regulation of Combination Products

Diane Mandell and *Joel Falk* explain the determination of regulatory jurisdiction for combination device, drug and biologic products.

The business strategy of combining medical devices with either a drug or biological product is increasingly being considered by many manufacturers as a means of either creating a completely unique product or extending the life of an established device. For example:

Determine who will review an application for necessary context to interpret regulations

- plain bone cement with a simple structural function has been improved by the addition of an antibiotic to control infection;
- a simple wound dressing designed to protect a wound site and encourage healing has been improved by the addition of antimicrobials to control infection; *and*
- coating a cardiovascular stent with a drug component intended to maintain vessel patency by minimising the occurrence of restenosis following stent implantation.

Once it has been determined which division of the regulatory agency will provide the overriding review of a combination product and whether or not consulting reviews from other divisions will be required, it will become paramount to understand and appreciate the regulations by which a product will be judged as well as the mindset of the responsible reviewers. The introduction of additional or unfamiliar regulations presents new challenges to the device manufacturer that must be taken into account as early as possible to assure success in approval.

In this article relating to the US regulatory environment, we will review the definition of a combination product; the factors that are considered in establishing primary jurisdiction; what to do when the primary jurisdiction is not obvious; and finally we will highlight new considerations that may be necessary for combination product manufacturers, which may never have been considered before.

Definition of a combination product

Scope of 'combination product' defined by the regulations

A combination product is a product composed of any combination of medical device, drug or biological product. These products usually involve cutting edge technologies under the jurisdiction of multiple regulatory agencies. Combination products are defined in 21 CFR Part 3, Subpart A, Section 3.2(e) as[1]:

1) a product with two or more regulated components that are physically, chemically or otherwise combined and produced as a single entity (i.e. drug/device, biologic/device, drug/biologic, or drug/device/biologic);
2) two or more separate products packaged together in a single package or as a unit;
3) a drug, device or biological product packaged separately that is intended for use only with an approved individually specified drug, device or biological product, where both are required to achieve the intended use or effect and that will be labeled as such upon approval; *or*
4) any *investigational* drug, device or biological product packaged separately that is for use only with another individually specified *investigational* drug, device, or biological product where both are required to achieve the intended use or effect.

In the US, the regulatory approval or clearance of combination products is fraught with the differences in regulatory requirements and the varying culture of contributing jurisdictions, and the submitter must consider each of the individual FDA Center's requirements in order to gain clearance or approval.

Characteristics of US review Centers vary markedly...

For some combination products, one Center will dominate the regulatory process (i.e. will have 'primary jurisdiction') and other Centers will contribute to a lesser extent (i.e. will have a 'consultative' role). For other products, Centers may share jurisdiction and will be considered 'collaborative reviewers.' It is the general perception that the Center for Devices and Radiological Health (CDRH) is the most 'streamlined' agency to work with, followed by the Center for Drug Evaluation and Research (CDER) and then the Center for Biologics Evaluation and Research (CBER). In September 2002, FDA announced the transfer of therapeutic biologic agents to CDER from CBER, with the goal of increasing efficiency of the review for these products. CDER plans to amass a staff of experts (some will likely be transferred from CBER) who can evaluate these new

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products. Some scientists remain hopeful that the reassignment of these products will make the approval process more streamlined for therapeutic biologics such as growth factors and monoclonal antibodies. Opinion and emotions are mixed both at FDA and in industry on the benefits of this approach.

...although their roles were defined in standard procedures in July 2002

The roles of each FDA reviewer and review Center have only been recently defined (July 2002) in the first version of the Manual of Standard Operating Procedures and Policies (SOPP), which serves as an internal document for reviewers of combination products[2]. The purpose of the SOPP is:

> *...to describe appropriate handling of the intercenter reviews of combination products, devices, drugs and biologics throughout the review process. The objectives are to improve intercenter communication on combination products as well as the timeliness and consistency of intercenter consultative and collaborative reviews.*

In any case, it is essential to have an early determination regarding whether a new product is considered a 'combination product,' because of the potential for increased time to market and costs for such a product. This aspect of product development is ideally considered early in the planning stages.

Determination of primary jurisdiction

Primary jurisdiction for a combination product can be determined in one of two ways:

Primary mode of action determines which Center leads a combination product review...

- the sponsor can consult FDA guidance documents and use their best judgment to establish which Center will have primary jurisdiction, and whether other Centers will have collaborative or consultative roles in the application process;
  or
- the sponsor can submit a Request for Designation(RFD) document to the FDA to formally request a decision for jurisdiction by the Agency.

Section 16 of the *Safe Medical Devices Act* (*SMDA*) of 1990 (Pub. L. 101-629) discusses the need for the FDA to designate a group that addresses issues for combination products, and describes how primary jurisdiction will be determined for combination products.

Historically, the component with the *primary mode of action* determines primary jurisdiction (*Federal Food, Drug, and Cosmetic Act*, Section 503(g)). For example, a medical or surgical kit that is marketed with a drug is considered a medical device (if the manufacturer is repackaging a marketed drug); the primary jurisdiction is with the Center for Devices and Radiological Health because the primary mode of action is device.

...but product risk may be the determinant in future

It is interesting to note that even though the primary mode of action determines which Center will take the lead review role at this time, the Agency has discussed the future possibility of using product risk as the determining factor in assigning product review jurisdiction.

Do-it-yourself determination of primary jurisdiction

In 1991, three InterCenter Agreements were written between Centers to help identify combination products and determine their status[3]. The InterCenter Agreements are limited by their age (publication date 1991), however they attempt to outline potential combinations of devices and drugs known at that time, and provide guidelines and special regulatory review requirements for the primary and secondary review Centers.

The InterCenter Agreement between CDRH and CDER provides examples of various combinations of devices and drugs. This document and the concepts presented are currently under revision by the Combination Products Program, as technology and issues have become more highly developed since the time of the original agreement.

Sponsors may self-determine primary jurisdiction, particularly where a precedent exists...

Determination of primary jurisdiction by the sponsor is possible, especially with certain combinations that have precedents and when the primary jurisdiction for the combination is specified in the FDA InterCenter Agreements, with the caveat that the Agency is undergoing a metamorphosis for some types of combination devices. For example, if a sponsor would like to manufacture a bone cement containing an antimicrobial agent, the guidance document for device/drug combinations specifies that CDRH is the market approval authority (i.e. primary jurisdiction) and CDER would be consulted as needed if the drug is not legally marketed in the US. An investigational device exemption (IDE) would be submitted to conduct clinical studies on this device/drug combination. If, on the other hand, the sponsor has a skin preparation pad containing antimicrobial agents, CDER would be the primary jurisdiction.

A second example is dental prophylaxis pastes. It has been determined, after receipt of several RFDs for dental prophylaxis pastes with drug components, that these pastes have the primary function of acting as a tooth cleaner and polisher (a device), with the drug component having a less important role, that of augmenting the primary function. Accordingly, these pastes have been determined to be regulated as devices within the Dental Devices Branch of CDRH, with consultation planned with CDER as needed. In the case of a manufacturer of a new dental prophylaxis paste, it would be reasonable for them to make the assumption that their new device will likely follow this pattern.

Request for determination

...but where determination is not straightforward there is also a formal request process...

Determining which jurisdiction will lead the review of some combination products is difficult. The Combination Products Program, in the Office of the Ombudsman under the direction of Mark Kramer, acts to formulate jurisdictional programmes and policies for combination products and to communicate new jurisdictional decisions to the community. The Ombudsman acts as the Product Jurisdiction Officer in cases where jurisdiction of a combination product is either in dispute or is difficult to assign.

Companies that have 'difficult' products to assign may file a Request for Designation (RFD), which results in a formal determination of the appropriate Center for primary assignment. The RFD process is outlined in 21 CFR Part 3; Section 3.7(c) provides the contents of the RFD document as listed in Figure 1[4].

Figure 1. Contents required in a Request for Designation of which Center leads review of a combination product, USA

Reference: 21 Code of Federal Regulations, Part 3, Section 3.7(c)

1. Sponsor identity
2. Product description, including:
   - i. classification, name of the product and all component products;
   - ii. common name of the product and all component products;
   - iii. proprietary name of the product;
   - iv. identification of components with premarket approval or if product has received an investigational exemption; also, the identity of all sponsors and any discussions regarding the use of this product as a component of a new combination product;
   - v. chemical, physical or biological composition;
   - vi. status and brief reports of developmental work, including animal testing;
   - vii. description of manufacturing and sources of all components;
   - viii. proposed use or indications;
   - ix. description of all known modes of action, the sponsor's identification of the primary mode of action, and the basis for that determination;
   - x. schedule and duration of use;
   - xi. dose and route of administration of drug or biologic;
   - xii. description of related products and their regulatory status; *and*
   - xiii. any other relevant information.
3. The sponsor's recommendation as to which agency component should have primary jurisdiction, with accompanying statement of reasons.

...which is best used prior to IND or IDE submission

Although an RFD can be submitted at any point during the regulatory process, it is advisable to submit this request early to avoid surprises (i.e. prior to submission of an Investigational New Drug or Investigational Device Exemption application).

The submitter should be aware of the primary mode of action and the potential risks and safety issues of the device prior to submitting an RFD. The submitter should be aware of precedents that support their position, especially since cross-Agency decisions may not be known by the Ombudsman. The focus of the RFD document is to provide FDA with the information necessary to make a determination, and present the submitter's preferred Center and their rationale for this choice, without relying too heavily on the InterCenter Agreements (which are in a state of flux). After submission of the RFD, the Product Jurisdiction Officer has 60 days to make a decision on the jurisdiction, but can request an extension.

As already mentioned, the main concern that a sponsor faces when determining the primary jurisdiction for a combination device is the continuous flux in the combination products' field. Jurisdictional updates are provided by the Agency to notify the regulatory community regarding new decisions. Two such Jurisdictional Updates have been published to date on drug-eluting cardiovascular stents, and dental prophylaxis pastes with drug components[5].

Additive needs of collaborating Centers can significantly increase sponsor workload

Incorporating another Center's product – key considerations

The collaboration of two Centers in the regulation of one combination device can be difficult because this process could result in the sponsor being asked to follow each Center's policies and that organisation's 'cultural' requirements. For example, when a medical device company prepares to submit an application for a device that has a drug component, such as a cardiovascular stent coated with a drug, the sponsor will likely be required to follow all of the usual regulatory guidelines for the medical device (stent), and in addition be required to apply Good Manufacturing Practices (GMPs) during the manufacture of the drug component (coating). This requirement adds significantly to the burden of the sponsor and is new to device manufacturers who are set up to follow Quality Systems Regulations (QSR) instead.

Each FDA Center, (CDRH, CDER, and CBER) has different regulations, policies, traditions and assumptions. It is commonly believed that CDRH represents a reviewing Center with a more streamlined approach, and sponsors with a device component tend to strive for primary device designation, structuring their RFD towards that goal. Nonetheless, even consultative review by other Centers is likely to create longer, more involved reviews. The submitter should expect questions, demands and approaches not common to their general experience as multiple Centers at FDA review their application. Standards of proof may be higher or different. Additionally, issues for some products are not faced by others and regulatory criteria may need to be clarified e.g. GMPs vs. QSRs.

Figure 2 shows important aspects of each Center (application type and other issues) that must be addressed when filing an application for a combination product between two or more Centers.

Figure 2. Filing a combination product application in the US – potential issues specific to each Center

Device (CDRH)	Drug (CDER)	Biologic (CBER)
Application types		
PMA 510(k) IDE	NDA IND	BLA IND
Other Issues		
Quality Systems Regulations Biocompatibility	Chemistry Manufacturing Controls Good Clinical Practices, GCP Good Laboratory Practices, GLP Pharmacokinetics (ADME)	Cell/tissue source Cell/tissue characterisation Safety testing Manufacturing, sterility

Abbreviations
ADME absorption, distribution, metabolism and excretion
BLA biological license application
NDA new drug application
PMA premarket approval application
510(k) 510(k) premarket approval application

An indication of the broad differences in Center expectations is laid out

The more difficult scenarios of combinations with no clear 'primary mode of action' are currently considered by FDA through open meetings with submitters and trade associations. Tissue-based technologies such as wound healing products that contain 'living human cells in a device matrix' are examples of products without a consistent policy. These products were originally considered as devices and assigned to CDRH (and the submitters prefer this designation); however, the Agency is leaning towards CBER as the primary review Center because of the noted importance of the biologic component of these devices. A public hearing was held on 24 June 2002 to assist in developing a consistent policy for the jurisdictional assignment of these products, with protest from industry over the potential reassignment of wound healing products to CBER.

Difficulties arise when there is no clear primary mode of action

Industry maintains the position that there is no primary mode of action for these products; thus, the contribution of the device and the biologic components are unable to be determined. The industry position is that the current device jurisdiction should be maintained until such time that the relative contribution of each component is elucidated. Further, industry urges FDA to maintain the current device designation for products already approved. At this meeting, FDA broached the potential for determining the Center jurisdiction based on the *risk of each component* rather than the current basis of *primary mode of action*. Such a change would have immense repercussions for certain combination products such as those with live cellular components.

Conclusion

Institution of jurisdictional requirements creates the potential for wide variability in the regulatory process for new combination products. Emerging technologies and evolving regulations should be considered when the sponsor establishes the primary jurisdiction based on precedents, or when submitting a Request for Designation to the Agency. Considerations of each of the three Centers may result in overlapping requirements in a combination product application to the FDA.

Regulatory process for combination products is inherently more uncertain

References

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