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FDA's Regulation of Combination Products: The Road Ahead

The Food and Drug Administration (FDA) applies different regulatory requirements to products depending upon whether they are medical devices, drugs or biologics. The agency has established different centers to handle these different types of products: for drugs, the Center for Drug Evaluation and Research (CDER); for devices, the Center for Devices and Radiological Health; for biologics, the Center for Biologics Evaluation and Research (CBER). Some products, however, combine products across jurisdictional lines, and these "combination products" have always posed a regulatory challenge for FDA.

In the past, FDA's handling of combination products has worked tolerably well, despite well-recognized shortcomings. The situation has begun to change, however, with the advent of an ever increasing number of important and innovative combination products, a trend that is only expected to accelerate in the years ahead. FDA has begun the process of updating its regulatory approach to handle the burgeoning challenge. This article describes the existing regulatory approach to combination products, some of the recognized problems with the existing approach, the recent steps FDA has taken to improve the process and some of the difficult challenges ahead.

Current Regulatory Approach

The FDA has regulated combination products for decades. Prior to 1990, the agency regulated such products on a case-by-case basis. Generally, the sponsor and FDA negotiated an ad hoc regulatory approach without explicit statutory guidance. In those discussions, the primary focus was most often whether the drug, biologic or device issues predominated.

As combination products multiplied and increased in complexity, the ad hoc approach was no longer satisfactory. In 1990, Congress enacted the Safe Medical Devices Act of 1990 (SMDA) (Pub. Law No. 101-629), which added section 503(g) to the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. §353(g)). This provision required FDA to designate a center—CDER, the Center for Devices and Radiological Health (CDRH) or CBER—with primary jurisdiction based upon the product's primary mode of action. The intent of section 503(g) was generally to add structure and consistency to FDA's regulation of combination products.

In FDA's implementing regulations, a combination product is defined as any one of the following:

- "A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
- 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;
- A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
- Any investigational drug, device or biological product packaged separately that according to its proposed

labeling 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."[1]

As required by the SMDA, FDA's implementing regulations assign jurisdiction over a combination product to CDRH, CDER, or CBER based upon the primary mode of action.[2] When one center receives jurisdiction in the review of a combination product application, it is considered the lead center but it will consult as appropriate with other centers.[3]

Even though the "primary mode of action" is the key statutory test for determining what center will take the lead in reviewing a combination product, neither the SMDA nor FDA's implementing regulation actually define the term. FDA did provide some guidance on this issue in the form of Intercenter Agreements between the three centers (CDER, CDRH and CBER), which were adopted in 1991.

The Intercenter Agreements outline the types of products and combination products that will be assigned to each Center and describe the product characteristics or medical indications that will require a consultative or collaborative review effort by the respective Centers. For example, the CDER/CDRH Agreement provides that a prefilled syringe will be investigated pursuant to an Investigational New Drug application and regulated by CDER using drug and device authorities as necessary.[4]

If there is uncertainty about jurisdiction over a combination product, many companies consult the product jurisdiction officers in the centers that potentially have responsibility for the product. These discussions are not binding on FDA, but are useful for providing an initial sense of the agency's likely position based upon historical precedent and the nature of the upcoming product.

If uncertainty remains, FDA regulations set forth a "Request for Designation" (RFD) procedure by which a sponsor submits a request and obtain a written and binding jurisdictional determination from the agency within 60 days. An RFD request is limited to 15 pages and, it identifies the sponsor, describes the product and sets forth the sponsor's legal and scientific argument as to which center should have jurisdiction.[5]

Problems With the Current Approach

The current approach has functioned tolerably well to date, but there are recognized problems. First, neither the statute nor the regulation defines "primary mode of action," which is the statutory test for determining the lead center for review of a combination product. The result has been a lack of clarity, consistency and predictability in jurisdictional decisions.

Second, the Intercenter Agreements were adopted in 1991 and they are increasingly out-of-date. This tendency toward obsolescence means that in some instances they do not reflect the actual regulatory practice that has developed over time, and in other cases they do not provide helpful guidance on newer technologies.

Third, the RFD process has not been entirely transparent. In particular, FDA has not publicized the 300 or so RFD decisions to date. Although it would be inappropriate in many cases for FDA to reveal particular products or sponsors, the failure to publicize even generic descriptions of the types of products and jurisdictional decisions has left companies very much in the dark.

Fourth, FDA's management of the combination products with regard to coordination and consultation between the centers has not always been consistently smooth. There has not been a consistent process for coordinating premarket review activities between the centers. For instance, the consulting centers sometimes treat consultations as a lower priority as compared to their primary product reviews. There also has been a lack of clarity as to the applicability of postmarket requirements. For instance, drugs are subject to the Good Manufacturing Practice regulation while devices are subject to the Quality System Regulation. Likewise, FDA regulates labeling and advertising somewhat differently for drugs and devices. FDA has not always clarified which requirements apply in the case of combination products.

Fifth, in some instances, product innovation has been stymied because of lack of cooperation among manufacturers. For example, an innovative drug delivery system may require a change in the drug labeling. If the drug manufacturer declines to cooperate, as has happened, the innovative drug delivery system may not be able to move forward in the FDA process. FDA, of course, has little control over the drug manufacturer's cooperation. Nonetheless, FDA has some discretion in determining whether a delivery system truly requires a labeling change and the data that will be required to support the change. This area is also one in which there has been confusion.

New Developments

In the Medical Device User Fee and Modernization Act of 2002, Pub. Law No. 107250, Congress established a new Office of Combination Products (OCP) within FDA Office of Commissioner to ensure prompt assignment of combination products to agency centers. This office is expected to add greater consistency and oversight to the regulation of combination products. OCP responsibilities include:

- Assigning an FDA Center to have primary jurisdiction for review of a combination product.
- Ensuring timely and effective premarket review of combination products by overseeing reviews involving more than one agency center.
- 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.

Pursuant to these responsibilities, the OCP has taken some important steps to improve the FDA's handling of combination products, including:

In July 2002, the OCP has adopted Standard Operating Procedures and Policies (SOPP) for Intercenter Review to help better manage and coordinate the process of intercenter review. This document was the outcome of an internal consultation and collaboration in which the OCP surveyed personnel in the centers to find out how they believed the process needs to be improved. For example, some reviewers in the consulting centers indicated that they were sometimes not brought into the process until a late stage. As another example, many FDA personnel felt that the center originating the consulting request should take more responsibility for providing focused issues and questions to be answered. The SOPP for Intercenter Review is intended to address these types of management issues.

The OCP has posted jurisdictional updates for dental prophylaxis pastes with drug components and drug eluting stents, in which recent RFDs are discussed and the agency's jurisdictional position on these types of products is described. It is not clear whether OCP intends to retroactively post information about older RFD decisions over the last ten years or how systematic OCP will be in posting new decisions. Nonetheless, the publication of this information appears to herald a new transparency in the RFD process that could greatly assist companies attempting to determine FDA's likely regulatory approach to a new combination product.

The OCP has held two public events devoted to improving the regulation of combination products. In November 2002, the OCP held a public meeting to solicit comments for improving the process of premarket review assignment and postmarket regulation of combination products. In July 2003, the OCP held a workshop that addressed regulatory and scientific challenges arising from innovative device delivery systems for drugs and biologics.

The Future

Seldom does adding another layer of bureaucracy improve the regulatory process. The OCP, however, appears to be a welcome exception. It has infused new energy, focus and coordination into FDA's regulation of combination products. The OCP has also made strides toward providing information to make the jurisdictional decision making process more transparent. It seems fair to predict that the OCP in the next year or two will go a long way toward resolving the lack of transparency and the management problems FDA has faced in past regulation of combination products. It seems much less likely that combination products in the future will fall between the cracks in the regulatory process.

Nonetheless, many thorny challenges remain. Most notably, OCP representatives have indicated that they are considering a definition of "primary mode of action." It is not clear whether the definition would be issued by regulation or in guidance. What is clear is that it will be very difficult to formulate a satisfactory definition of this term. To be successful, the OCP will have to devise a definition that guides FDA toward consistent, predictable and sound jurisdictional decisions. If such a definition were easy to formulate, it would have been done long ago. It may be that new legislation is necessary to establish some practical criteria for deciding which center should have primary jurisdiction instead of the nebulous primary mode of action test.

Another challenge arises when the manufacturer of an innovative drug delivery system is unable to obtain cooperation from the drug (or biologic) manufacturer. As an example, if an innovative drug delivery system requires a new route of administration or a slight reformulation of the drug (or both), FDA is likely to insist upon essentially the full complement of data normally required in a New Drug Application (NDA) in order to support the drug's safety and effectiveness. If the drug manufacturer cooperates by providing access to existing Drug Master File, IND, and NDA data submitted to support the original approval, the delivery system manufacturer may be able to obtain a significant reduction in new testing requirements. On the other hand, if the drug manufacturer is not cooperative, FDA legally cannot consider the existing data and is likely to require the delivery system manufacturer to perform a great deal of safety and efficacy testing that may be largely redundant with the testing done to support the original drug approval.

In the past, FDA has suggested that one solution would be for the drug delivery system manufacturer to file an NDA based upon public literature under Section 505(b)(2) of the FD & C Act. Unfortunately, FDA has seldom been able to implement the Section 505(b)(2) approach in a practical manner that actually reduces the testing burden on the device delivery system manufacturer. It remains to be seen whether FDA can make this approach work.

As a final example, there is still significant confusion for drug and delivery device combination products about how best to coordinate separate approvals or whether separate approvals are needed. In some cases, FDA has allowed the filing of an NDA with CDER accompanied by a "pullout" device premarket approval (PMA) application or 510(k) submission that is reviewed concurrently by CDRH. The hope is that all of these applications will be approved on the same day,

but FDA does not offer any such guarantee, and it has not always happened. In other cases, FDA has essentially incorporated the delivery device into the drug NDA approval as a unitary application. CDER reviews the entire application but consults with CDRH as necessary.

FDA has provided little guidance on the decision about which approach to pursue (i.e., pullout application versus unitary application). To some extent, the difficulties arise because FDA must apply statutory requirements intended for separate drug and device products to a unitary product that combines a drug and device. No amount of guidance from FDA will resolve all of the difficulties inherent in this situation. Rather, it may be necessary for Congress to create a unitary statutory approval mechanism that is explicitly intended and designed for combination products.

In summary, we are moving into a new era where the combinations of drugs, devices and biologics will present extremely difficult regulatory challenges for FDA. The new FDA commissioner, Mark McClellan, MD, has made the rational regulation of combinations a high priority. However, if FDA is to avoid the stifling of important new combination products, there will have to be not only a high level of cooperation among FDA and industry, but also a high level of cooperation between FDA centers. Hopes abound that the new OCP will be able to assist in streamlining and expediting a process that has not worked optimally for many years with new and important combination products stuck in a regulatory maze that has been very difficult to navigate.

NOTES:

1. 21 CFR Part 3.2(e). It is worth noting that, under this definition, a product can be labeled for concomitant use with another product without being a combination product. For example, a contrast agent labeled for use with a general class of imaging devices that does not require any change in the labeling for the imaging devices would not be a combination product.
2. 21 CFR Part 3.4(a).
3. *Federal Register* 56 (21 November 1991).
4. Ibid, Chapter VII.A.1(b).
5. 21 CFR Part 3.7.

This article is based, in part, on a presentation by Jonathan S. Kahan, JD, to the FDA Public Workshop: Innovative Systems for Delivery of Drugs and Biologics—Scientific, Clinical, and Regulatory Challenges, Bethesda, MD, 8 July 2003. Kahan and Jeffrey K. Shapiro, JD, are partners in the Food, Drug and Medical Device Practice Group at Hogan & Hartson, LLP, a Washington-based law firm.