

Working Through the US Rules for Combination Products

Suzanne O'Shea explains how the Food and Drug Administration determines the regulatory path for combination products, and identifies areas where creativity and flexibility might pay off.

Some of the most innovative and cutting-edge new healthcare products are those that combine, in some conjugation or other, drugs, devices and biologics. These products, known as combination products, generate excitement over their therapeutic potential, but also anxiety over the challenges of melding two or even three different product types and their corresponding regulatory requirements. For manufacturers looking to take a combination to the US market, there exists a potential for creativity and flexibility in developing a regulatory path through the Food and Drug Administration that is often overlooked by sponsors. This article explains how the FDA determines the regulatory path for combination products and identifies some of the areas where creativity might pay off.

Creation of combination product rules

Combination products were formally recognised in the US through the enactment of the Safe Medical Devices Act of 1990, which added Section 503(g) to the Federal Food, Drug, and Cosmetic Act. The amendment was made to address various difficulties that sponsors were experiencing when seeking approval of a product that combined a drug and a device, a drug and a biologic, or a biologic and a device.

Prior to the amendment, there had been scope for uncertainty as to which of the FDA regulatory paths a combination product manufacturer should follow. As mandated by the act, the agency provides separate schemes for regulating drugs, biologics and devices. Each statutory scheme takes into account the differing characteristics of the three product groups to ensure that each type of product is adequately reviewed and regulated with regards to its safety and effectiveness. This statutory approach is reflected in the FDA's organisational structure, which includes a Center for Drug Evaluation and Research, a Center for Biologics Evaluation and Research and a Center for Devices and Radiological Health. For many years, these centres have operated as virtually separate organisations. They operate from different office complexes that are separated geographically (although the FDA headquarters are now in the process of moving to one campus in White Oak, Maryland)¹. They use different procedures that reflect their individual statutory schemes. They also exhibit individualised cultures that tend to reflect the degree of risk perceived to be attached to the type of product being regulated.

These distinctions tended not to cause a problem when sponsors sought approval of a single-entity, or noncombination, product, and when they were familiar with the statutory and regulatory provisions governing the product's review and the process and culture of the reviewing centre.

For combination products, however, it was a different story. It was unclear which premarket approval scheme ought to apply, and whether one or both centres concerned with the product types should have oversight over the product. Sponsors found themselves trying to manage intercentre interaction on their own. They may also have received contradictory advice from different centres; had conflicting requirements imposed on them; or found themselves falling through the cracks between centres. In addition, difficulties were magnified by the fact that, while sponsors were frequently familiar with one centre and its culture, they were having to navigate a different centre that was very foreign to them.

The 1990 Safe Medical Devices Act amendment required the FDA to assign combination products to one lead agency centre for review and regulation based on the product's primary mode of action². The amendment does not define the terms "combination product" or "primary mode of action," but states that nothing in the statutory provision prevents the FDA from using "any agency resources" necessary to ensure adequate review of products' safety, effectiveness or substantial equivalence³. This means that, while one centre will have primary jurisdiction for reviewing and regulating the product, another centre may be consulted.

Responsibility for assigning combination products to a lead agency centre was initially given to the Office of the Chief Mediator and Ombudsman and was then transferred over to the Office of Combination Products, which was created statutorily in 2002⁴. The OCP has made significant

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progress in clarifying and resolving issues that arise throughout the lifecycle of combination products. In addition, it is expected to issue, in the near future, proposed rules on adverse event reporting and current good manufacturing practices for combination products⁵.

Recent experience

In FY 2007, the agency reviewed marketing and investigational applications for 333 combination products

In fiscal year 2007, the FDA reviewed marketing and investigational applications for 333 combination products. Of these, 14 original new drug applications were submitted to CDER, and 166 investigational new drug applications were submitted to both CDER and CBER. Four device premarket approval applications, 109 510(k) premarket notifications, 36 investigational device applications, and one humanitarian use device application, were submitted to CDRH. The remaining three applications were for biologic licences, which were submitted to CBER.

Of the 333 original combination product applications, 142 were classified as CDER-led, 148 were classified as CDRH-led and 43 were classified as CBER-led.

Manufacturers are concerned that involving two centres will slow down reviews

A frequent concern among combination product manufacturers is that the review will be slower because two centres will be involved. This concern, however, is not always well-founded. Premarket applications for combination products are subject to the same user fee performance goals as those for single entity products. According to the OCP Performance Report for 2007, all NDAs and BLAs and nearly all 510(k)s covering combination products were reviewed within the relevant user fee time frames⁶.

The OCP also tracks consultations between centres to ensure that they are completed in a timely manner. In FY 2007, the OCP tracked 390 intercentre consultations.

Finally, the OCP routinely reminds combination product makers of its availability for advice throughout the life cycle of a product. Sponsors have found the OCP to be very willing to help work out the logistics of a review in which two or more centres participate.

Definition of combination product

Shortly after the enactment of Section 503(g) of the act, the FDA issued regulations defining four different types of combination products. Under 21 CFR 3.2(e), a combination product may be comprised of:

- two or more regulated entities that are physically or chemically combined into one integrated product, such as a drug-eluting stent;
- two or more separate products of different types packaged together in a single package, such as a drug packaged together with a delivery device;
- a new drug, device or biologic labelled for use with an already approved, separately marketed drug, device or biologic, such as a delivery device labelled for use with an already approved, separately marketed drug or biologic, when upon approval of the new product, the labelling of the approved product would need to be changed (eg to reflect a change in intended use, dosage form, strength, route of administration or significant change in dose); and
- two investigational products where both are required to achieve the intended effect.

Products comprised of two drug components, two device components or two biologic components are not combination products under these regulations. In such cases, both components of the product are regulated by the same agency centre and there is no need to assign it to one lead agency centre. In 2003, the FDA transferred many therapeutic biologic products from CBER to CDER for review and regulation. Therefore, some drug-biologic products may meet the definition of a combination product, but do not need a jurisdictional determination because CDER regulates both components⁷.

Assignment of combination products

The FDA has issued numerous combination product guidance documents

In 1991, the FDA issued three intercentre agreements, which provided information on the way many products were assigned to CDER, CBER and CDRH at the time those documents were written. For many years, these documents provided useful guidance on product assignment. However, they have never been updated and have, over time, lost currency as new types of products have been developed⁸. Instead of updating the intercentre agreements, the FDA has issued numerous combination product guidance documents and has posted many jurisdictional determinations on the OCP's website⁹.

A regulation on product assignment came in 2005, when the FDA issued 21 CFR 3.2(m). This defines the primary mode of action of a combination product as the single mode of action that is expected to make the greatest contribution to the overall intended therapeutic effects of

the combination product. For a drug-eluting stent, for example, the FDA has determined that the device component makes the major contribution to the therapeutic effect of the product as a whole by holding a vein open, while the anti-inflammatory drug enhances the effectiveness of the stent by preventing restenosis. Because the product's primary mode of action is attributable to the device component, drug-eluting stents are assigned to CDRH for review and regulation. CDRH consults with CDER in the review of such products.

However, it is not always possible to determine which one of two modes of action will provide the greater contribution to the overall therapeutic effect of a combination product. In such cases, the agency will assign the product to the agency centre that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole. Where there are no other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole, the agency will assign the product to the agency centre with the most expertise related to the most significant safety and effectiveness questions presented by the product¹⁰.

For example, the preamble to the final rule hypothesised a contact lens (device) that corrects vision and is also impregnated with a drug to treat glaucoma. In such a case it is not possible to say that either the vision-correcting mode of action or the glaucoma-treating mode of action is clearly primary. Therefore, according to the preamble, if the FDA were presented with a product like this, it would first determine whether any other contact lens/glaucoma drug products had been reviewed by the agency. If no other such products had been submitted to the FDA for review, the agency would assign the product to the centre with the most expertise related to the most significant safety and effectiveness questions presented by the product. In this case, because the glaucoma drug would likely present the most significant safety and effectiveness questions, the product would be assigned to CDER for review and regulation.

The FDA has a system of deciding which centre should regulate a combination product in unclear cases

Obtaining a jurisdictional determination

The OCP has made public on its website a great deal of information about its jurisdictional determinations. A review of this information is a useful first step in determining the likely assignment of a combination product. The OCP is often willing to discuss informally the assignment of combination products. In a few cases, a jurisdictional determination can be made in the absence of a formal request.

Sponsors that want a formal and binding jurisdictional determination must submit to the OCP a written Request for Designation (RFD). The RFD was created by the FDA to make formal jurisdictional determinations in cases where the agency centre that ought to lead jurisdiction over a combination product is unclear or in dispute. There is no form for an RFD, but the information it must contain can be found listed in the regulations and must be limited to 15 pages or less. The RFD gives a sponsor the opportunity to make a recommendation to the FDA on the assignment of the product to a lead centre. The FDA has 60 days to respond to an RFD and if it fails to respond within this period, the sponsor's recommendation automatically takes effect. To date, the FDA has not failed to issue a response to an RFD within 60 days¹¹.

The statute requires that the FDA only assigns a lead agency centre through the RFD process. In practice, however, the agency clarifies whether the product will be reviewed under the drug or device provisions of the act, or the biologic licensing provisions of the Public Health Service Act¹², and provides a contact person within the reviewing centre for further information.

The OCP is often willing to discuss informally the assignment of combination products

More than one marketing application

In most cases, the FDA requires only one marketing application for combination products. It has stated that only one application is permissible for combination products that are physically or chemically combined into one integrated product. However, combination product regulations state that the designation of one agency lead centre does not preclude consultations by that centre with other agency centres or, in appropriate cases, the requirement by the FDA of separate applications¹³. Thus, in certain cases, the FDA can require two marketing applications for a combination product¹⁴.

But while the rules allow the FDA to ask for more than one marketing application, they also raise the possibility that manufacturers can themselves request that their product be reviewed under two marketing applications when it would be advantageous to do so. For example, a combination product comprised of a drug and a drug delivery device would, under the primary mode of action theory, be assigned to CDER for review and regulation, most likely under the new drug provisions of the FD&C Act. However, it might be advantageous to the sponsor to have the drug component reviewed by CDER under an NDA, and the device component reviewed by CDRH under the device provisions of the act. It may be that the sponsor intends to use similar

The rules raise the possibility for sponsors to request that their product be reviewed under two marketing applications

technology for additional devices to deliver other drugs, and so would prefer to obtain a 510(k) for the delivery device in order to ease the review of future delivery devices. Additionally, the sponsor may wish to take advantage of the ability to make changes to the device quickly under the 510(k) scheme. On the other hand, submitting two applications for a drug and delivery-device system might require increased co-ordination between two centres and this possibility must be considered when deciding whether to request the use of two marketing applications.

A sponsor might want to submit two applications to take advantage of drug exclusivities

Other possible reasons behind a sponsor's wish to submit two marketing applications include the ability to take advantage of orphan drug product exclusivity or other drug exclusivities, or when more than one sponsor is involved in the production of the combination product. When considering whether to request the use of more than one application, sponsors should find it useful to consider all the different types of marketing applications that could be used, including BLAs for further manufacture and 505(b)(2) new drug applications.

Unless the FDA believes there is a need for two marketing applications, it will ordinarily instruct sponsors to submit a single marketing application. There is, therefore, onus on the sponsor to suggest the use of two marketing applications in situations where it would be useful. Sponsors should try to anticipate concerns the FDA might have over the use of more than one application (eg how would postapproval changes be handled?) and develop a method for addressing those concerns.

The RFD process can also be used to request the use of more than one application – sponsors can use the recommendation section to explain how they see the two applications will be submitted and reviewed. For example, it might be helpful for sponsors to describe how their data and information would be reviewed under each marketing application. Although the FDA is required only to designate the lead agency centre in RFDs, the OCP has shown a willingness to respond to sponsors' requests about the use of more than one marketing application in RFDs.

Finally, it should be noted that even if two applications are submitted to two centres, one of the centres will still be designated as the lead centre.

Combination products through labelling

Products designated as combination products through labelling present challenges and opportunities to the FDA and industry

Products that are designated as combination products through labelling present challenges and opportunities to both the FDA and industry. Under 21 CFR 3.2(e)(3) of the FD&C Act, a new drug, device or biologic product intended for use with an already approved, individually specified drug, device or biologic product may be a combination product when the labelling of the already approved product "needs to be changed" upon approval of the new product. This is known as a "cross labelling" or "mutually conforming labelling" issue.

For example, suppose a sponsor of a unique intravenous delivery device wishes to label the device for use with a drug product (even another sponsor's drug) that is currently labelled for subcutaneous administration. Under the regulations, if the labelling of the drug would "need to be changed" upon approval or clearance of the new delivery device, the two products would be considered a combination product. If the two products are considered a combination product, then, in all likelihood, the primary mode of action of that product would be attributable to the drug component, and the product would be assigned to CDER for review and regulation. This would result in the new drug delivery device also being reviewed by CDER under the new drug provisions of the act – an outcome that a delivery device manufacturer is unlikely to want. This example does not address the difficulty the device sponsor may have in persuading the drug sponsor to submit a supplemental NDA to effectuate a labelling change to provide for the intravenous administration of the drug. It is frequently the case that sponsors of approved products do not wish to submit the supplement required to amend their product's labelling, leading to an inability on the part of the FDA to approve or clear the new product.

To date, the agency has not clarified when the labelling of the already approved product needs to be changed (the conditions referenced in 21 CFR 3.2(e)(3) are listed as examples, not as circumstances requiring an amendment to current labelling) and this uncertainty has perhaps led to sponsors of new products intended for use with already approved products to decide against their commercialisation. Opportunity lies within the uncertainty, however, as sponsors can suggest to the FDA reasons why the labelling of the already approved product does not need to be changed, thereby taking the new product out of the combination product realm.

Sponsors might be able to take a new product out of the combination product realm

Alternatively, there may be instances when a sponsor of a new product intended for use with an already approved product would prefer his/her product to be a combination product. For example, suppose the sponsor of a new drug intended it to be used with an already marketed device, and that the two products were considered a combination product, with the primary mode of action of the product being attributable to the device component. In such a case, the sponsor of the new drug might argue that the device labelling would need to be changed to reflect the use of

the drug with the device, thereby resulting in CDRH being designated as the lead agency centre for reviewing and regulating the new drug. (Such an approach would require that the sponsor of the device agreed to amend its product's labelling upon approval of the new drug.)

In May 2005, the OCP held a conference on cross labelling, in an effort to clarify the application of 21 CFR 3.2(e)(3)¹⁵. To date, no further clarifications of this regulation have been issued. In the meantime, the RFD process can be used to recommend to the FDA whether or not a product should be considered a component of a combination product through labelling. To the greatest extent possible, sponsors should anticipate the FDA's concerns about requiring the labelling of an approved product to be changed, or concluding that it does not need to be changed, and meet those concerns in the RFD.

FDA concerns about changing or not changing labelling should be anticipated by the sponsor and met in the RFD

Conclusion

US regulations for combination products were created to ease difficulties arising out of two FDA centres having responsibility over one product. While the FDA has little discretion over the assignment of a lead agency centre based on the primary mode of action of the product, there are other areas where flexibility and creativity are possible with combination products. The possibility of using more than one marketing application and that a new product may or may not be a combination product through labelling (and therefore assigned to an agency centre based on a primary mode of action) are just two areas where sponsors might be able to recommend to the FDA creative regulatory pathways through the agency.

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