Chapter 8

Combination Products

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Key Points

- **A combination product comprises two or more different types of regulated components. It can be a drug/device, a biologic/device, a drug/biologic, or a drug/device/biologic.**
- **The Safe Medical Devices Act of 1990 directs FDA to assign review of a combination product to an agency center based on the product's primary mode of action (PMOA).**
- **The PMOA is the single mode of action that provides the most important therapeutic effect of the combination product. Drug-coated vascular stents, for example, are regulated as devices because the mechanical scaffolding of the stent provides the most important therapeutic action.**
- **A sponsor of a combination product can submit a request for designation where the jurisdiction of the reviewing center is unclear or in dispute.**
- **FDA has issued a guidance describing the assessment of user fees for combination products.**

What the Statute and Regulations Say

A combination product is one that has multiple characteristics. It could be a drug/device, a biologic/device, a drug/biologic, or a drug/device/biologic. Increasingly in the past decade there have been more and more products that have been designated by the Food and Drug Administration (FDA) as combination products. An example might be a device whose purpose is to deliver a drug to a patient, or a product used during surgery.

Products that combine two products of the same type are not regarded as combination products. For example, a fixed combination drug product comprising two or more drug ingredients in a single dosage unit is not a combination product. Similarly, products comprising two or more devices, or two or more biological products, are not combination products. Products comprising a drug and a cosmetic, or a drug and a dietary

supplement, are also not considered combination products, although they raise some of the same issues as combination products.

The Safe Medical Devices Act of 1990 addresses the threshold combination product issue: when a product comprises more than one type of product, which FDA center will review and regulate it?

The first statutory reference to combination products occurred in the Safe Medical Devices Act of 1990. The statute addresses the threshold combination product issue: when a product comprises more than one type of product, which FDA center will review and regulate it? The statute directs the agency to assign combination products to an agency center for review based on the product's primary mode of action (PMOA), but significantly contains no definition of ''combination products'' or PMOA:

> The Secretary shall designate a component of the Food and Drug Administration to regulate products that constitute a combination of a drug, device, or biological product. The Secretary shall determine the primary mode of action of the combination product. If the Secretary determines that the primary mode of action is that of—
>
> (A) a drug (other than a biological product), the persons charged with premarket review of drugs shall have primary jurisdiction,
>
> (B) a device, the persons charged with premarket review of devices shall have primary jurisdiction, or
>
> (C) a biological product, the persons charged with premarket review of biological products shall have primary jurisdiction.
>
> FDCA § 503(g); 21 U.S.C. § 353(g)

Regulations issued shortly thereafter included the following definition(s) of combination products:

- A product comprising 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 (21 C.F.R. § 3.2(e)(1)). Examples include drug-coated stents, an implantable replacement joint coated with a growth factor, and a monoclonal antibody with a therapeutic drug attached.
- Two or more separate products packaged together in a single package or as a unit and comprising drug and device products, device and biological products, or biological and drug products (21 C.F.R. § 3.2(e)(2)). An example would be a kit containing a drug and a device applicator.
- 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) (21 C.F.R. § 3.2(e)(3)). An investigational device intended to deliver an already approved drug product in a new way for a new use would fit this definition.

- 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 (21 C.F.R. § 3.2(e)(4)). An investigational device intended to deliver an investigational new drug would be deemed a ''combination product'' under this definition.

The statute does not address the statutory provisions under which a combination product is to be regulated. In practice, combination products are almost always regulated under the type of application ordinarily submitted to the center with jurisdiction over the product. In other words, combination products assigned to the Center for Drug Evaluation and Research (CDER) are ordinarily reviewed under the new drug provisions of the Federal Food, Drug, and Cosmetic Act (FDCA); combination products assigned to the Center for Devices and Radiological Health are ordinarily reviewed under the device provisions; while combination products assigned to the Center for Biologics Evaluation and Research (CBER) are ordinarily reviewed under the licensing provisions of the Public Health Service Act or the device provisions of the FDCA.

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An exception to the above is FDA's final rule ''Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco to Protect Children and Adolescents.'' FDA asserted that it had the discretion to choose the premarket approval authority for combination products that provides the best public health protection (61 Fed. Reg. 44395, 44402 (Aug. 28, 1996)). In practice, combination products are almost always reviewed under the premarket approval authority ordinarily used by the lead reviewing center.

Primary Mode of Action and Assignment of a Lead Agency Center

Intercenter Agreements

In 1991, CBER, CDER, and CDRH entered into three Intercenter Agreements (ICAs): a CBER–CDER Intercenter Agreement, a CBER–CDRH Intercenter Agreement, and a CDER–CDRH Intercenter Agreement. Although they differ in content, format, and scope, the ICAs share the common purpose of explaining how various categories of both combination and single-entity medical products were classified and assigned at the time the agreements were written in 1991. The ICAs constitute guidance that is not binding on the public or the agency.

The usefulness of Intercenter Agreements (ICAs) is becoming increasingly limited as new products are developed that were not envisioned when the ICAs were established.

At the time the ICAs were written, they were the major jurisdictional statements issued by the agency, but their usefulness is becoming increasingly limited as new products are developed that were not envisioned when the ICAs were established. Since 1991, FDA has continued to classify and assign many new products not specifically covered by the ICAs. The body of jurisdictional decisions has therefore grown significantly, and over time, the ICAs have become incomplete statements.

In 2006, the agency published a *Federal Register* notice in which it concluded that while the CDER–CDRH and CBER–CDRH ICAs continue to provide useful nonbinding guidance about the assignment and classification of products, the CBER–CDER ICA was rendered almost completely out of date by the transfer of many therapeutic biological products from CBER to CDER in 2003. For these reasons, the agency proposed to continue the CDER–CDRH and the CBER–CDRH ICAs in effect, and to rescind the CBER–CDER ICA. As of the writing of this chapter, this proposal had not been finalized.[1]

Primary Mode of Action

As noted above, the FDCA requires that combination products be assigned to an agency center on the basis of the product's PMOA, but does not include a definition of PMOA. In 2005, FDA amended the combination product regulations to include a definition of PMOA.

The amended regulations begin by defining mode of action as ''the means by which a product achieves an intended therapeutic effect or action. For purposes of this definition, 'therapeutic' action or effect

includes any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body'' (21 C.F.R. § 3.2(k)).

PMOA is defined as ''the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product'' (21 C.F.R. § 3.2(m)).

In many cases, this definition suffices to determine a combination product's PMOA. The preamble to the final rule provides several examples, including a drug-coated vascular stent. A vascular stent provides a mechanical scaffold to keep a blood vessel open while the drug is slowly released from the stent to prevent the buildup of new tissue that would re-occlude the artery. This product has two modes of action—the device mode of action contributed by the stent and the drug mode of action contributed by the drug coating. The stent itself provides the most important therapeutic effect of the product, while the drug augments the effectiveness of the stent. Accordingly, drug-coated stents are generally assigned to CDRH for review and regulation under the device provisions of the act.

In contrast, a drug-eluting disc, which is surgically implanted and contains a drug that is slowly released for prolonged, local delivery of chemotherapeutic agents to a tumor site, also has device and drug modes of action. In this case, however, the chemotherapeutic drug makes the most important contribution to the therapeutic effect of the product. Products like this are assigned to CDER for review and regulation under the new drug provisions of the FDCA.

In some cases, FDA has not been able to determine which component makes the major therapeutic contribution to the product. For example, consider a contact lens that corrects vision and also contains a drug that will be delivered from the lens to treat glaucoma. This hypothetical product has both drug and device modes of action, but the two modes of action are independent of one another, and neither appears to be subordinate to the other. In cases like this, where it is impossible to say that one component provides the most important therapeutic action of the product, the agency follows an assignment algorithm set out in the regulations.

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The first step of the algorithm is to determine whether one agency center regulates other combination products presenting similar questions of safety and effectiveness with regard to the combination product as a whole. In this case, CDER regulates glaucoma drugs presenting questions of safety and effectiveness similar to those presented by the drug in the combination product, and CDRH regulates devices presenting questions of safety and effectiveness similar to those presented by the contact lens

in the combination product but neither agency center regulates combination products that present questions similar to those presented by both the contact lens and the glaucoma drug.

When no agency center regulates combination products presenting questions of safety and effectiveness with regard to the combination product as a whole, the agency proceeds to the second step of the algorithm; the agency considers which center has the most expertise related to the most significant safety and effectiveness questions presented by the combination product. In this case, the most significant safety and effectiveness questions are related to the characterization, manufacturing, and clinical performance of the drug component, while the safety and effectiveness questions raised by the vision-correcting contact lens are considered more routine. As a result, the corrective contact lens with a glaucoma drug product would be assigned to CDER for review. If a second manufacturer were to submit a marketing application for a similar product, the similar product would be subsequently assigned to CDER under the first step of the algorithm. (21 C.F.R. § 3.4(b).)

Requests for Designation

A request for designation is a formal process by which the sponsor of a combination product requests that FDA assign the product to a center for review when it is unclear or disputed as to which center has jurisdiction over the product.

A request for designation (RFD) is the formal process by which a sponsor of a combination product requests that the agency assign a combination product to a center for review when it is unclear or in dispute as to which center has jurisdiction over the product. An RFD is limited to fifteen pages, and contains summary information about the product and its intended use. FDA recommends that an RFD be submitted as soon as sponsors have enough information about the product to enable FDA to make a decision.

An RFD is also to contain the sponsor's assessment of the modes of action of the components of the combination product, as well as the sponsor's description of the product's PMOA. Sponsors may include data on these points if it is useful to the determination of the product's modes of action and PMOA. The sponsor is also given the opportunity to recommend which center should have jurisdiction over the product.

By statute, the agency is allowed sixty days to respond to RFDs. The agency's decision is in the form of a designation letter. Decisions made in an RFD letter are unique in two respects. First, the agency may change these decisions without the consent of the sponsor only to protect the public health or for other compelling reasons. Second, if the agency does not issue a designation letter in response to an RFD within the sixty-day time period, the sponsor's recommendation as to assignment of the product takes effect. The agency rarely, if ever, fails to issue an RFD letter within the sixty-day time frame.[2]

Consults and Collaboration

Even though one agency center is designated as the lead, the other center will likely be involved in the review. In general, participation by the other relevant agency center is either a consultative review or a collaborative review. The RFD designation letter will state the role of the other center.

A consult occurs when one center requests advice from another center on a specific question or issue. A collaboration occurs when two or more centers have primary review responsibilities, generally for a defined portion of a submission. Regulatory and scientific decisions will be made by the management of each center for that portion of the review assigned to it, including the decision to approve or refuse to approve the product.

FDA has issued a Standard Operating Procedure (SOP) for the Intercenter Consultative/Collaborative Review Process.[3] The objective of this SOP is to improve intercenter communication on combination products, as well as the timeliness and consistency of intercenter consultative and collaborative reviews.

A frequent concern about consults and collaborations is that they will slow down the review process. To allay such concerns, the SOP states that ''all consulted and collaborating reviewers should be held accountable and receive credit for thorough and timely expert reviews and advice. Every effort should be made to meet the due date identified by the request originator.'' The SOP also stresses the importance of frequent, ongoing communication between the primary reviewer and the consulting or collaborative reviewer.

COMBINATION PRODUCT ISSUES

Adverse Event Reporting

FDA has not issued a regulation covering the reporting of adverse events for combination products. The agency has, however, issued for comment purposes only, a concept paper on postmarket safety reporting for combination products.[4]

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The postmarket safety reporting requirements for drugs, biologics, and devices share many similarities. For example, each requires the reporting of deaths and serious adverse events, as well as the submission of periodic or follow-up reports. In general, appropriate postmarket safety

reporting is achieved by following the requirements for the type of marketing application used for approval or clearance of the combination product. For example, a drug/device combination product approved under a new drug application would be subject to the postmarket reporting requirements for drugs.

There are some differences in the adverse event reporting requirements of drugs, devices, and biological products, however, and if combination products were subject only to the postmarket reporting requirements associated with the marketing application, some reporting requirements would not apply. For example:

- Both drug and device regulations require that deaths or serious injuries be reported. In addition, device postmarket safety regulations require reporting of device malfunctions where no death or serious injury occurred, but the device would be likely to cause or contribute to a death or serious injury if the malfunction were to recur (21 C.F.R. § 803.20(3)(ii)). Reporting for drugs and biological products does not include an analogous requirement to report a product failure. For some combination products containing a device constituent part that is regulated under the drug or biological product provisions of the act, it may be necessary to also comply with the device requirements should an adverse event occur that is attributable to the device constituent part.

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- The device regulations also require reporting within five days of a reportable event that requires remedial action to prevent an unreasonable risk of substantial harm to the public health, as well as reportable events for which FDA makes a written request. (21 C.F.R. § 803.10(c)(2)(i).) For some combination products containing a device constituent part that are regulated under the drug or biological product provisions of the act, it may be necessary to also comply with the device requirements if the adverse event is attributable to the device constituent part.
- For drugs and biological products, regulations require reporting of adverse events that are both serious and unexpected within fifteen days of the sponsor's receipt of information about the event. (21 C.F.R. § 314.80(c).) Device postmarket safety regulations require reporting of any serious injury within thirty days. For some combination products containing a device and a drug or biological product, that are regulated under the device provisions of the act, it may be necessary to also comply with the drug and biological product requirements when the adverse event is attributable to the drug or biological product constituent part.
- The biological product regulations require a written report within seven days of any blood-related death (21 C.F.R. § 606.170). For some blood-containing combination products regulated under the drug or device provisions of the act, it may be necessary to also comply with this requirement.

Current Good Manufacturing Practices

While FDA has issued a draft guidance on current Good Manufacturing Practices (cGMPs) for combination products, as of this writing FDA had not issued a proposed or final regulation covering the application of cGMPs (including 21 C.F.R. Parts 210 and 211 for drugs and biological products and Quality System Regulations (QSRs) for devices, 21 C.F.R. Part 820.)[5]

Current Good Manufacturing Practices and QSRs are intended to ensure that drugs; biological products; human cells, tissues, and cellular and tissue based-products; and devices are made properly. Each set of regulations, however, is somewhat different because each is tailored to the characteristics of the types of products for which they were designed. Each set of regulations contains certain express or specific requirements that may be only generally expressed in the other set of regulations. For example, the cGMP regulations for drugs and biological products specifically require calculation of yield and stability while QSRs contain more general design validation provisions. Similarly, QSRs have detailed Corrective and Preventive Action (CAPA) provisions, while cGMPs contain more general production record requirements.

Under the draft current Good Manufacturing Practices (cGMP) guidance, each drug, biological product, or device constituent part of a combination product, taken individually, is subject only to its governing cGMP regulations until it is actually combined with another type of constituent part to form a combination product.

Under the draft guidance, each drug, biological product, or device constituent part of a combination product, taken individually, is subject only to its governing cGMP regulations until it is actually combined with another type of constituent part to form a combination product. For example, when the constituent parts of a combination product are separately marketed, such as a new device intended for use with an individually specified, already approved drug product marketed by a different manufacturer, the device constituent part would be subject only to the QSRs, while the drug constituent part would be subject only to the cGMP regulations.

On the other hand, for combination products in which the constituent parts are physically, chemically, or otherwise combined or co-packaged, it generally should not be necessary for manufacturers to maintain two separate manufacturing systems to ensure compliance with both sets of regulations during and after joining the constituent parts together. Compliance with both sets of regulations during and after joining the constituent parts of a combination product can generally be achieved by using either the cGMP or QSRs because it should be possible to develop and implement a practice that complies with a more specific requirement in one set of regulations even while using the more general requirement framework included in the other set of regulations.

The following chart, from the draft guidance, identifies key provisions of the cGMP and QSRs that differ in their specificity. FDA recommends that manufacturers of constituent parts that are co-packaged or physically,

chemically, or otherwise combined carefully consider these provisions during and after joining the constituent parts to ensure compliance with both cGMP and QSRs.

Key Current Good Manufacturing Practice Provisions to Consider During and After Joining Together Co-Packaged and Single-Entity Combination Products

If The Operating Manufacturing Control System Is Part 820 (QS Regulation)		If the Operating Manufacturing Control System Is Part 210/211 (cGMP Regulation)	
Carefully Consider These Specific cGMP Requirements	Title	Carefully Consider These Specific QS Requirements	Title
§ 211.84	Testing and approval or rejection of components, drug product containers, and closures	§ 820.30	Design controls
§ 211.103	Calculation of yield	§ 820.50	Purchasing controls
§ 211.137	Expiration dating	§ 820.100	Corrective and preventative actions
§ 211.165	Testing and release for distribution		
§ 211.166	Stability testing		
§ 211.167	Special testing requirements		
§ 211.170	Reserve samples		

According to the draft guidance, it may be important to consider other specific requirements to ensure compliance with both cGMP and QSRs depending upon the particular combination product. An example is aseptic control assurance for drug and biological product constituent parts unable to withstand terminal sterilization.

In the draft guidance, FDA recommends that manufacturers present information to the agency during the development phase about how they intend to achieve compliance with both sets of regulations during

and after joining the constituent parts together of proposed combination products that will have constituent parts that are physically, chemically, or otherwise combined, or that will be co-packaged. For example, FDA recommends that a pre-investigational new drug (pre-IND) or pre-investigational device exemption (pre-IDE) meeting include a discussion of the sponsor's implementation of cGMPs, including consideration of risks of the combination product, its technology, and any anticipated postmarket development and postapproval changes. FDA recommends that the sponsor include all critical manufacturers in these discussions and include information on critical steps that may be conducted at source/contract firms and any special testing. FDA's Office of Combination Products is available as a resource to sponsors in the resolution of cGMP concerns.

Number of Applications

According to FDA regulations, ''the designation of one agency component as having primary jurisdiction for the premarket review and regulation of a combination product does not preclude . . . in appropriate cases, the requirement by FDA of separate applications.'' (21 C.F.R. § 3.4(c).) This regulation suggests that most of the time combination products will be reviewed and regulated under one application.

FDA has also issued a concept paper intended to clarify the number of marketing applications necessary for approval or clearance of a combination product.[6] According to the concept paper, while a combination product is assigned to an agency center based on the product's PMOA, the PMOA does not automatically determine the type of marketing application that will be used. Depending on the type of product, approval or clearance could be obtained either through a single marketing application, or through separate marketing applications for the individual constituent parts of the combination product.

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For most combination products, a single marketing application should be sufficient to ensure product safety and effectiveness. FDA review of a combination product under a single application addresses the combination product as a whole and its constituent parts.

Although two applications for a combination product have rarely been required, the concept paper notes that there are some circumstances in which two applications could be necessary to ensure safety or effectiveness of the combination product. According to the concept paper, two applications might be required in the following circumstances:

- when the constituent parts are separate and complex products;
- when one constituent part has uses beyond the combination product;

- when a Biologics License Application for further manufacture is appropriate to ensure the identity, safety, purity, and potency of certain biological products when the product as a whole is being regulated under the drug or device provisions;
- to effect labeling revisions for a constituent part that is already approved for uses that do not include the proposed combination product indication;
- to maintain regulatory consistency.

Additionally FDA, under some circumstances, may accept two applications from the manufacturer when one would suffice to ensure the safety and effectiveness of the product. FDA recognizes that certain regulatory mechanisms (such as new drug exclusivity or orphan drug benefits) are associated only with certain types of marketing applications and that sponsors may wish to derive specific benefits that accrue under a particular application. In addition, when two manufacturers are involved in the development and manufacture of a combination product, each manufacturer may prefer its own application. The concept paper requests stakeholder perspectives on appropriate FDA responses when sponsors desire to have multiple applications.

User Fees

Congress first authorized FDA to collect fees from companies that manufacture drugs and biological products under the Prescription Drug User Fee Act of 1992 (PDUFA), and from companies that manufacture devices under the Medical Device User Fee and Modernization Act of 2002 (MDUFMA). FDA has issued a guidance describing the assessment of user fees for combination products.[7]

In general, combination products reviewed under one application will be subject to the user fees associated with that type of application.

In general, combination products reviewed under one application will be subject to the user fees associated with that type of application. For example, a biologic/device or a drug/device combination product for which a device premarket approval (PMA) application is required would be subject to the PMA fee under MDUFMA.

In instances where one application would suffice but the sponsor(s) elect to submit two applications covering the constituent parts of a combination product, FDA believes that the user fees associated with both applications should be payable. Although sponsors may still be eligible for fee waivers or reductions, FDA assesses the two fees because review of two applications when one would suffice places an extra burden on FDA resources.

On the other hand, when FDA requires two applications for a combination product, sponsors are encouraged to consider submitting a request

for user fee waiver or reduction. In particular, according to the guidance, FDA will look closely at whether a PDUFA ''barrier to innovation'' waiver may be applicable to reduce the additional fee burden associated with FDA's requirement for two marketing applications.

Both PDUFA and MDUFMA provide waivers or reductions of fees associated with the submission of applications by small businesses, although the eligibility standards and amount of the fee waiver or reduction differ. Sponsors of combination products requiring two applications should consider applying for the small business waiver or reduction under PDUFA and/or MDUFMA if they meet the qualification criteria.

Both PDUFA and MDUFMA provide waivers or reductions of fees associated with the submission of applications by small businesses, although the eligibility standards and amount of the fee waiver or reduction differ.

Other than certain specific situations, such as marketing applications submitted by small businesses, standard MDFUMA fees are required for nearly all device marketing applications. In contrast, PDUFA provides for waivers or reduction of fees where:

- Such waiver is necessary to protect the public health.
- The assessment of the fee would present a significant barrier to innovation because of limited resources or other circumstances.
- The fees to be paid by such person will exceed the anticipated present and future costs incurred by the Secretary in conducting the process for the review of human drug applications for such person.

Combination products that incorporate cutting-edge, innovative technologies that hold promise for advancing patient care may also be eligible for waiver or a reduction of fees as FDA believes that assessment of two marketing application fees could represent a significant barrier to its development. To be eligible for the ''innovative combination product'' waiver under PDUFA's ''barrier to innovation because of . . . other circumstances'' provision, FDA considers the following factors:

- the combination product as a whole is innovative;
- FDA is requiring two fee-bearing marketing applications for the product;
- the applications request approval only of the two components of the combination product for use together (i.e., neither application includes an independent use for that constituent part of the combination product); and
- the applicant does not qualify for a small business waiver or have limited resources.

FDA considers the following factors in determining whether a combination product is innovative for purposes of the waiver application:

- the product addresses an unmet medical need in the treatment, diagnosis, or prevention of disease and therefore provides significant, meaningful advantage over alternatives;

- factors such as whether one of the two applications includes a new molecular entity, has been designated as a priority drug, is eligible for expedited device review, or has been granted fast track status; and
- the existence of treatment alternatives (which would weigh against deciding that a product is innovative).

For innovative combination products requiring two applications, FDA would expect to reduce PDUFA fees as follows in appropriate situations:

- For products requiring a MDUFMA application and a PDUFA application, FDA would expect to reduce the PDUFA fee by the amount of the MDUFMA fee. Thus a sponsor would pay the full MDUFMA fee associated with the MDUFMA application, and a PDUFA fee reduced by the amount of the MDUFMA fee. The total amount paid would be the equivalent of one PDUFA fee.
- For products requiring two PDUFA applications (for combination products comprising a drug constituent part and a biological product constituent part), FDA would expect to reduce each PDUFA fee by half. In such a case, the total amount paid would be equivalent to one PDUFA fee.

The ''innovative combination product'' waiver provides for a possible waiver only of application fees; the waiver is not applicable to annual product and establishment fees.

According to the guidance, the ''innovative combination product'' waiver provides for a possible waiver only of application fees; the waiver is not applicable to annual product and establishment fees. FDA reviews requests for waivers of product and establishment fees, as well as requests for waivers or reductions of application fees not qualifying for the ''innovative combination product'' waiver, under criteria applicable to both combination and noncombination products.

FDA's Office of Combination Products

Immediately following formal creation of the combination products category in 1990, the task of designating a lead agency center for review and regulation of combination products was assigned to the Office of the Chief Mediator and Ombudsman in the Office of the Commissioner. Over the years, a number of concerns have been raised about combination products, including concerns about the consistency, predictability, and transparency of the assignment process; issues related to the management of the review process when two or more FDA centers had review responsibilities for a combination product; and lack of clarity about the postmarket regulatory controls applicable to combination products.

FDA's Office of Combination Products (OCP) was established on December 24, 2002, as required by MDUFMA, to address such concerns. The law gives OCP broad responsibilities covering the regulatory life cycle of combination products. As outlined in MDUFMA, the responsibilities of OCP include:

The Medical Device User Fee and Modernization Act of 2002 gives FDA's Office of Combination Products broad responsibilities covering the regulatory life cycle of drug-device, drug-biologic, and device-biologic combination products.

- 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; and
- submitting annual reports to Congress on the office's activities and impact.

By most accounts, OCP has been successful in meeting these objectives.[8] In particular, the annual report to Congress provides a great deal of detail about the activities of the OCP.

ENDNOTES

1. The most recent information relative to these ICAs is available at www.fda.gov/oc/combination/intercenter.html.
2. Additional details about RFDs can be found in 21 C.F.R. §§ 3.7 – 3.9, and in a guidance document issued by the Office of Combination Products, ''How to Write a Request for Designation (RFD)'' available at www.fda.gov/oc/combination/Guidance-How%20to%20Write%20an%20RFD.pdf.
3. Available at www.fda.gov/oc/ombudsman/intercentersop.pdf.
4. See www.fda.gov/oc/combination/adveventconcept.html.
5. For the most up-to-date information, see www.fda.gov/oc/combination/OCLove1dft.html.
6. See www.fda.gov/oc/combination/singlesepconpaper.html.
7. See www.fda.gov/oc/combination/userfees.html.
8. For further information, please see the OCP website at www.fda.gov/oc/combination.