

FY 2006



PERFORMANCE REPORT TO CONGRESS

for the

Office of Combination Products

as required by the

***Medical Device User Fee and
Modernization Act of 2002***

Commissioner's Report

I am pleased to submit the Food and Drug Administration's Fiscal Year (FY) 2006 Annual Report to Congress for the Office of Combination Products (OCP). This report includes the third full year of data since OCP was established as mandated by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA), enacted on October 26, 2002.

Combination products are therapeutic and diagnostic products that combine elements of drugs, devices, and/or biological products. The Food and Drug Administration (FDA) is receiving significantly more combination products for review as technological advances continue to merge product types and blur the historical lines of separation between FDA's medical product centers. Because combination products involve components that would normally be regulated under different types of regulatory authorities, and frequently by different FDA Centers, they also raise challenging regulatory, policy, and review management issues. The differences in regulatory pathways for each component can impact the regulatory processes of all aspects of the product life cycle, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, and post-approval modifications.

OCP has made significant progress in enhancing the transparency and predictability of the combination product lead Center assignment and review process. OCP has facilitated interactions between industry and FDA to clearly delineate regulatory paths, and implemented processes to ensure the timely and effective review, and consistent and appropriate postmarket regulation of combination products. One large industry trade association wrote us following a recent survey of its members to congratulate OCP on the progress made. The letter stated that "OCP has done an excellent job in meeting the goals outlined in MDUFMA in spirit and in practice."

Combination products will continue to become more complicated as new technologies emerge and existing technologies mature. OCP, therefore, will continue to focus on the most important issues relating to combination products and actively assist industry and FDA reviewers in understanding this complex regulatory area.

FDA looks forward to continued success in meeting the unique challenges in the review and regulation of combination products.

Andrew von Eschenbach, M.D.
Commissioner of Food and Drugs

Executive Summary

FDA established OCP on December 24, 2002, in response to MDUFMA. The mission of OCP is to ensure the prompt assignment of combination products (drug-device, biologic-device, drug-biologic, or drug-device-biologic products) to FDA Centers, the timely and effective premarket review of such combination products, and consistent and appropriate postmarket regulation of these products.

This document presents OCP's annual report to Congress. OCP activities for FY 2006 highlighted in this report include the following:

- **Prompt Assignment of Combination Products.** OCP published a number of documents relating to the assignment of combination products in FY 2006. OCP published two *Federal Register* notices, one describing FDA's preliminary review of agreements, guidance documents, and practices specific to the assignment of combination products. The other *Federal Register* notice announced that FDA was transferring responsibility of catheter lock-flush solution combination products from Center for Drug Evaluation and Research (CDER) to Center for Devices and Radiological Health (CDRH). OCP published a guidance document clarifying what is meant by the minimal manipulation of structural tissue. Several jurisdictional updates were published, including those for breath test combination products, and approximately 50 additional capsular descriptions of selected jurisdictional decisions were published. Additionally, OCP continued to provide prompt Request for Designations (RFD) decisions. OCP issued 26 combination product RFD assignments in the last fiscal year. One hundred percent of these assignments met the 60-day decision time requirement.
- **Timely and Effective Premarket Review.** In FY 2006, OCP continued to make significant contributions to the premarket review of combination products by directly facilitating complex review challenges. OCP also continued to provide help and support to internal and external stakeholders by serving as an informal resource for combination product regulatory and process issues. OCP published a guidance document outlining early development considerations for innovative combination products. Other OCP activities relating to premarket review include the organizing of a number of working groups to address specific regulatory issues pertaining to combination products. Specific issues addressed in FY 2006 include autoinjectors and new products intended to be used with another sponsor's already approved product.
- **Combination Product Review.** FDA received 231 original applications for combination products in FY 2006. This amount represents a decrease of 15 percent from the 273 original applications for combination products in FY 2005. However,

the number of intercenter consulting reviews increased to 335 for FY 2006 from 275 in FY 2005. This amount represents a 22 percent increase in intercenter consults. Recent examples of approved combination products can be found at <http://www.fda.gov/oc/combination/approvals.html>.

- **Consistent and Appropriate Postmarket Regulation.** In FY 2006, OCP announced its intention to promulgate two regulations to help ensure the consistent and appropriate postmarket regulation of combination products. These proposed rules would clarify current good manufacturing processes and postmarket safety reporting requirements. Additionally, OCP chaired and convened a working group considering postmarketing changes to combination products.
- **Additional Activities and Impacts.** OCP continued to conduct internal and external outreach activities through a variety of educational and informational presentations for both FDA staff and stakeholders. These activities were intended to foster greater efficiency of the combination product development and review process by enhancing understanding of the complex regulatory issues encompassing the review of combination products.

Throughout FY 2006, OCP endeavored to ensure the prompt assignment of combination products to Centers, the timely and effective premarket review of such products, and the consistent and appropriate postmarket regulation of these products. These activities help provide patient access to innovative technologies and address unmet medical needs through the timely delivery of safe and effective combination products to the public.

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Introduction

On October 26, 2002, Congress enacted MDUFMA. By amending the Federal Food, Drug, and Cosmetic Act, MDUFMA provided FDA with new responsibilities, resources, and challenges. Among other things, MDUFMA required FDA, not later than 60 days after the date of enactment, to establish an office within the Office of the Commissioner “to ensure the prompt assignment of combination products to agency centers, the timely and effective premarket review of such products, and consistent and appropriate postmarket regulation of” combination products. As required by MDUFMA, FDA established OCP within the Office of the Commissioner on December 24, 2002. Information about OCP, including the authorizing text of the MDUFMA amendments, can be found at <http://www.fda.gov/oc/combination>.

MDUFMA also requires FDA to submit an annual report to Congress on the activities and impact of OCP. This document fulfills this requirement for FY 2006.

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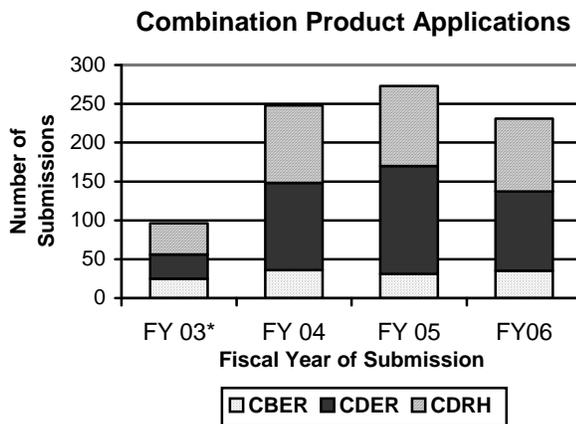
Overview of Combination Products

Combination products are increasingly being developed to enhance the safety and effectiveness of conventional medical products. These products are defined by any of the following criteria as in 21 CFR 3.2(e):

- (1) Products 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;
- (2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
- (3) A drug, device, or biological product packaged separately that, according to its investigational plan or proposed 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;
- (4) 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.

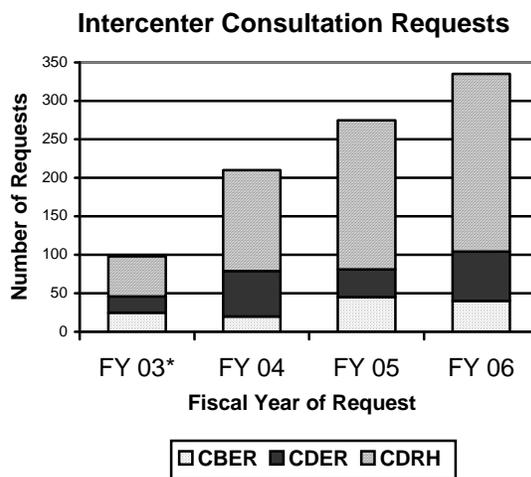
More and more combination products are incorporating cutting-edge, novel technologies that hold great promise for advancing patient care. Beyond drug-eluting stents and inhaled insulin, breakthrough new products approved after OCP was established, combination products may include drug-delivery systems, pharmacogenomic drug-device combinations, nanotechnology, gene therapy systems and products for many other diagnostic and therapeutic treatments. Some estimates forecast that the combination products market could increase from approximately \$6 billion in 2004 to nearly \$10 billion by 2009 (“Regulations, Guidances in the Works for Rapidly Advancing Combination Products Sector”; *Food and Drug Letter*, Issue No. 717, February 11, 2005). Others estimate that combination drug delivery products alone are growing at an annual rate of 14 percent, an increase expected to add up to \$38 billion in yearly sales by 2008 (“Drug-Device Makers Can Expect New Guidance”; *AAMI News*, February 2005). Furthermore, BCC Research Inc., estimates that the total global value of the drug-device combination products market will increase from \$5.4 billion in 2004 to \$11.5 billion in 2010 (“Drug-Device Combinations”, *BCC Research*, June 2005).

The number of combination products submitted for review decreased in FY 2006; however, the number of intercenter consultation requests continued to increase. The number of combination products submitted for review in FY 2006 decreased from FY 2004 and FY 2005 levels (see graph to the right). The majority of this decrease was in the number of combination products submitted for review to CDER.



* Numbers do not represent all of FY 2003. FDA began data collection on April 1, 2003.

More Centers were included in combination product reviews. Despite the decrease in the number of combination products submitted in FY 2006, the number of intercenter consultation requests on combination products increased by 22 percent (275 to 335, see graph below). Since combination products involve components (biologics, drugs, and devices) that would normally be regulated under different types of regulatory authorities, and frequently by different FDA Centers, they also raise challenging regulatory, policy, and review management issues. The differences in regulatory pathways for each component can impact the regulatory processes of all aspects of the product life cycle, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, and post-approval modifications. In addition, combination products increasingly use state-of-the-art, innovative technologies that challenge existing regulatory and scientific knowledge.



Mandated Functions of the Office of Combination Products

FDA established OCP within the Office of the Commissioner’s Office of International Activities and Strategic Initiatives (OIASI) on December 24, 2002. MDUFMA established broad responsibilities for OCP that cover the regulatory life cycle of drug-device, drug-biologic, and device-biologic combination products, and include product jurisdiction decisions and specific premarket review and postmarket processes. However, the primary responsibilities for scientific review and regulation of combination products

remain in one of three product Centers – the Center for Biologics Evaluation and Research (CBER), CDER, or CDRH – to which they are assigned by OCP. Specifically, the statute (503(g)(4)(B-F)) requires OCP to:

1. Promptly assign a Center with primary jurisdiction for a combination product.
2. Ensure the timely and effective premarket review of combination products, by overseeing the timeliness of and coordinating reviews involving more than one Center.
3. Ensure the consistency and appropriateness of postmarket regulation of combination products.
4. Resolve disputes regarding the timeliness of premarket review of combination products.
5. Review and update agreements, guidance documents or practices specific to the assignment of combination products.

OCP also serves as a focal point for addressing combination product issues raised by FDA reviewers and industry, and works with the Centers to develop guidance and/or regulations to clarify the regulation of combination products.

In addition, the Office of the Commissioner consolidated the product jurisdiction program in June 2003, giving OCP responsibility for FDA action on all RFDs submitted by industry in accordance with 21 CFR Part 3. This includes requests for classification and assignment of a particular product as a biological product, device, or drug, as well as requests for assignment of combination products.

OCP Organizational Structure

As of September 30, 2006, OCP is staffed by seven permanent full-time positions. In addition to a Director of OCP, these positions include an Associate Director (Medical Officer), a Product Assignment Officer, a Product Classification Officer, a Senior Advisor, a Scientific Reviewer (Biologist and Emerging Leader Intern), and a Program Support Specialist. In terms of staff turnover, two staff members retired during the past year and two new staff members joined OCP. Work plans provide for an eventual projected staffing size of 11 positions when financial resources to support such needed expansion are available. The office is located at: 15800 Crabbs Branch Way, Suite 200, HFG-3, Rockville, MD 20855, (301) 427-1934, fax (301) 427-1935, email: combination@fda.gov.

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Report on FY 2006 OCP Activities and Impacts

This section reports the activities and impacts of OCP in the assignment of combination products and in coordinating the review and regulation of combination products for FY 2006. Additionally, this section provides a performance assessment for combination product applications acted on in FY 2006. Consistent with the mandated functions of OCP, data highlighted in the following section include:

- Prompt Assignment of Combination Products
- Timely and Effective Premarket Review
- Consistent and Appropriate Postmarket Regulation
- Effective Resolution of Review Disputes

Unless otherwise noted, all performance data in this section are as of September 30, 2006.

Overview of Activities and Impacts

OCP reports specific activities and impacts in this section. Much of the workload data were obtained through the use of a new internal tracking database for documenting OCP's activities. The following summary illustrates the scope and breadth of OCP activities throughout the past fiscal year.

- **The database contains over 600 records of OCP activities for FY 2006.**¹ These records include approximately 270 activities conducted with internal stakeholders and approximately 350 with external stakeholders. Most of the stakeholders contacted OCP for assistance through email and telephone. The primary purpose of the contacts were jurisdiction/assignment (approximately 150 contacts); premarket review issues (approximately 230 contacts); postmarket regulation issues (approximately 50 contacts); and other issues within OCP's scope of responsibility (approximately 200 contacts) for an approximate total of 630 contacts. The majority of the contacts (approximately 390 of 630) involved combination products, and approximately 75 percent of these were for drug-device combinations. OCP participated in approximately 120 meetings with internal and/or external stakeholders in FY 2006.

¹ These activities are in addition to a wide range of OCP activities associated with its review of and response to Requests for Designation.

Prompt Assignment of Combination Products

MDUFMA requires OCP to promptly assign to a Center primary jurisdiction for a combination product and to review and update agreements, guidance documents, or practices specific to the assignment of combination products. OCP is required to assign premarket review responsibility for combination products based on the product's primary mode of action (PMOA).² By submitting an RFD, a company may obtain a formal FDA determination of a combination product's PMOA and of assignment of the lead Center for the product's premarket review and regulation.³ FDA will make its jurisdictional determination within 60 days of filing the RFD, or the sponsor's recommendation of the Center with primary jurisdiction will become the assigned Center.⁴ In addition, companies and Centers often informally request assistance from OCP in working out difficult jurisdictional issues not raised in an RFD submission.

OCP FY 2006 activities and impacts related to the assignment of combination products are as follows:

- **Issued all (100 percent) assignments, due as of September 30, 2006, within the 60 days provided by 21 CFR 3.8.** RFD performance data for the assignment of combination products in FY 2006 is found in the section of this report entitled "Report on FY 2006 OCP Requirements, Prompt Assignment of Combination Products."
- **Published a *Federal Register* notice requesting comments on FDA's review of agreements, guidance documents, and practices specific to the assignment of combination products.** Section 503(g)(4)(F) of the Federal Food, Drug, and Cosmetic Act (the act) requires FDA to review each agreement, guidance, or practice that is specific to the assignment of combination products to agency centers and to determine whether the agreement, guidance, or practice is consistent with the requirements of the act. In carrying out the review, FDA is to consult with stakeholders and directors of the Centers, and then determine whether to continue, modify, revise, or eliminate such an agreement, guidance, or practice. FDA completed its initial review of relevant agreements, guidances, and practices, and has consulted with directors of the Centers. The notice, published in the September 28, 2006, *Federal Register* (71 FR 56988), provides the preliminary results of OCP's review. The notice explains that FDA reviewed the 1991 intercenter agreements (ICAs) and preliminarily determined that they are generally consistent with the requirements of section 503(g) of the act, in that the principles used to assign combination products described in the ICAs are based on a product's PMOA. In particular, FDA has preliminarily determined that the CDER-CDRH and CBER-CDRH ICAs continue to provide helpful nonbinding guidance. FDA proposes to continue the CDER-CDRH and CBER-CDRH ICAs, with the understanding that they should not be independently relied upon as the most current, complete jurisdictional statements. The notice summarizes the actions taken by FDA to increase the transparency

² This is in accordance with section 503(g)(1) of the Act (21 U.S.C. 353(g)(1)).

³ The RFD process, including the information required in a RFD submission, is outlined in 21 CFR Part 3.

⁴ This is by operation of section 563 of the Act (21 U.S.C. 360bbb-2).

of jurisdictional decision making, and to help put the ICAs in proper context. The notice further explains that the 2003 administrative transfer of many therapeutic biological products from CBER to CDER has rendered the CBER-CDER ICA out-of-date, and so FDA preliminarily proposes to withdraw the CBER-CDER ICA. Upon receipt and review of stakeholder comments on FDA's preliminary review, FDA will publish another *Federal Register* notice announcing its determination. The *Federal Register* notice is available at www.fda.gov/OHRMS/DOCKETS/98fr/E6-15967.pdf.

- **Published a *Federal Register* notice transferring primary review responsibility for catheter lock-flush solutions combination products from CDER to CDRH.** The notice, published in the August 17, 2006, *Federal Register* (71 FR 47499), announced that FDA is transferring primary responsibility for the regulation of heparin catheter lock-flush solution products from CDER to CDRH. Heparin catheter lock-flush solution products are intended to enhance the performance of intravascular catheters, devices that are inserted into a patient's vascular system for short-term use to sample blood, monitor blood pressure, or administer fluids intravenously. Heparin catheter lock-flush solutions are periodically inserted into and stored within the catheter to keep the catheter unobstructed and to prevent blood from clotting within the catheter between uses. These products are combination drug-device products. Prior to the mid-1990s, heparin catheter lock-flush solution products were regulated under the new drug and abbreviated new drug provisions of the act, with CDER serving as the lead FDA review component. However, more recently, based on several jurisdictional determinations by FDA for specific products, applications for catheter lock-flush solutions containing an anticoagulant, such as heparin, or antimicrobial components have been assigned to CDRH and regulated under the device provisions of the act. The notice explains that FDA is transferring the applications for heparin catheter lock-flush solution products that were in CDER to reflect these more current jurisdictional determinations. The transfer of lead review responsibility to CDRH is based on FDA's determination that the PMOA for these heparin catheter lock-flush solution products is for the device part of the combination (see related jurisdictional update below). The transfer provides consistency and efficiency in the regulation of these combination products by treating like products similarly. The *Federal Register* notice is available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/E6-13509.pdf>.
- **Published a jurisdictional update describing the assignment of drug-device catheter lock-flush solutions.** The jurisdictional update explains that the solution component of catheter lock-flush solution products (for example, water or saline solution) acts by physically occupying space within the catheter and exerting pressure on the patient's circulating blood. In this way, the patient's blood is prevented from backfilling into the catheter and clotting. FDA concluded that, in acting in this manner, the solution component of the product meets the definition of a device in that it affects the structure or function of the body, and does not achieve its primary intended purposes through chemical or metabolic action within or on the patient's body. FDA also determined that in these cases, the anticoagulant or antimicrobial component of the catheter lock-flush solutions act chemically on microorganisms and/or prevent thrombotic occlusions with the catheter. Therefore, these ingredients meet the definition of a drug in that they are intended to affect the structure or function of the body. Review responsibility for these

products was assigned to CDRH for review and regulation under the device provisions of the act, based on FDA's determination that the PMOA of the products was attributable to their device components. The jurisdictional update is available on the OCP website at www.fda.gov/oc/combinatoin/catheter.html.

- **Published a guidance document entitled “Guidance for Industry and FDA Staff: Minimal Manipulation of Structural Tissue - Jurisdictional Update.”**
This guidance document provides information about the classification of products as human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulated solely under section 361 of the Public Health Service Act (PHS Act). The document discusses FDA’s current thinking on the meaning of the phrase “minimally manipulated” contained in 21 CFR 1271.10(a)(1), and defined (“minimal manipulation”) at 21 CFR 1271.3(f), as it applies to structural tissue. FDA regulations define “minimal manipulation” for structural tissue as “processing that does not alter the original relevant characteristics of the tissue relating to the tissue’s utility for reconstruction, repair, or replacement.” FDA has received several RFD’s requesting a determination of whether or not certain HCT/Ps will be regulated solely under section 361 of the PHS Act based on the manipulation the product undergoes during processing. The guidance document explains that, for purposes of determining whether a structural tissue product is minimally manipulated, a tissue characteristic is “original” if it is present in the tissue of the donor. A tissue characteristic is “relevant” if it could have a meaningful bearing on how the tissue performs when utilized for reconstruction, repair, or replacement. A characteristic of structural tissue would be relevant when it could potentially increase or decrease the utility of the original tissue for reconstruction, repair, or replacement. The document explains that, once FDA has determined, based on the data and information before it, that processing has altered an original characteristic of a structural tissue, and that the characteristic is relevant in that it has a potential effect on the utility of the tissue for reconstruction, repair, or replacement, FDA considers the tissue to be more than minimally manipulated and not eligible for regulation solely under section 361 of the PHS Act. In such a case, the structural tissue will be regulated as a drug, device, and/or biological product under the Federal Food, Drug, and Cosmetic Act and/or section 351 of the PHS Act. The guidance document is available on the OCP website at www.fda.gov/oc/combinatoin/manipulation.html.
- **Published a jurisdictional update concerning breath test combination products.** Since 1992, FDA has received numerous RFDs for combination product diagnostic breath tests in which the drug component is an isotope-labeled substrate and the device components capture and/or analyze exhaled breath for detection of labeled carbon dioxide or other gases. These RFDs have addressed the use of breath test combination products for the diagnosis of *H. pylori*, gastric emptying disorders, carbohydrate malabsorption, intestinal bacterial overgrowth, insulin resistance, liver function, for monitoring enzyme activity, for assessment of small intestinal function, and for use in pharmacological research. In some cases, such as diagnosis of *H. pylori*, the substrate is metabolized by bacteria present in the stomach or gut; in others, the substrate is metabolized by the patient when a particular disease or condition is present. Upon metabolism of the substrate, labile metabolites are exhaled that can be uniquely traced to the substrate. Thus, for example, the presence, absence, or rate of release of isotope-

labeled carbon dioxide in exhaled breath is intended to be indicative of the presence or absence of the disease or condition in question. In these cases, FDA determined that the PMOA of such combination products was attributable to the device components' role in the in-vitro diagnosis of the disease or condition in question, while the drug component plays a secondary role in acting as the diagnostic substrate. FDA assigned CDRH to be the lead Center for reviewing these products. The jurisdictional update explains that, in a recent case, FDA determined that two marketing applications were not necessary for a diagnostic breath test combination product. In this recent case, FDA determined that the premarket approval (PMA) provisions of the Act (21 CFR 814) would enable FDA to determine the safety and effectiveness of both the device and drug components of the combination product. CDRH will consult or collaborate with CDER, as appropriate, on issues such as chemistry and manufacturing, pharmacology and toxicology, and clinical issues related to the drug component. This jurisdictional document is published on the OCP website at www.fda.gov/oc/combination/breathtest.html.

- **Published 55 additional capsular descriptions of selected jurisdictional decisions.** These descriptions of selected RFD decisions serve to update the examples provided in the ICAs and are intended to improve the transparency of the jurisdiction process. In selecting which jurisdictional determinations were appropriate to summarize and make public, OCP considered the extent to which the product could be suitably described, the extent to which the existence and description of the product or similarly described products has been made public, and other related factors. The descriptions are grouped by Center and cover both combination and non-combination products. OCP will continue to update the list of capsular descriptions as new decisions are made and as information on these products becomes publicly available. The current list contains 253 capsular descriptions, and is available on the OCP website at www.fda.gov/oc/combination/determinations.html.
- **Published eight additional RFD decision letters for products that have been approved or cleared.** The RFD decision letters, posted on the OCP Internet site, were redacted to remove trade secret and confidential commercial information. Publishing these letters, which generally include FDA's reasoning in making the jurisdictional determination, is intended to provide additional transparency on the jurisdictional decision making process. Fifty letters are currently posted, and OCP plans to post additional letters on a regular basis. The letters are available on the OCP website at www.fda.gov/oc/combination/rfd.html.
- **Continued the activities of the working group that is exploring the development of a definition of "chemical action," a key determinant of whether a product is a device or a drug.** One of the distinctions between the statutory drug and device definitions is that a device does not achieve its primary intended purposes through chemical action within or on the body, and is not dependent on being metabolized to achieve its primary intended purposes. The goal of this working group is to further clarify what is meant by "chemical action within or on the body" contained in the statutory definition of a device. Such clarification should be helpful to sponsors and FDA in determining whether a product meets the definition of a drug or a device.

- **Continued to monitor and enhance internal processes to ensure the prompt and efficient review of RFDs.** OCP conducted a review of its practices, specific to the assignment of combination products, to ensure that they are in compliance with the requirement of section 503(g)(4)(B) of the act that the agency promptly assign a combination product to an agency center with primary jurisdiction for the product. As explained in the September 28, 2006, *Federal Register* notice (71 FR 56988) on FDA's review of agreements, guidance documents and practices, FDA has refined its practices to ensure that jurisdictional assignments are made promptly. The notice explains that all RFD requests submitted from inception of OCP to March 31, 2006, were completed within the statutory 60-day review period. FDA's average processing time for RFDs for combination products during this period was 37.7 days, with a median of 40 days and a range of 11 to 59 days. The notice explains that FDA has preliminarily determined that the current FDA RFD assignment practices are consistent with the requirement for the prompt assignment of combination products contained in section 503(g)(4)(B) of the act. FDA plans to continue the process improvements needed to maintain the prompt assignment of combination products, and plans to continue to work to refine its processes further.
- **Continued monthly product jurisdiction meetings for the exchange of information between OCP jurisdictional and assignment specialists, and CBER, CDER, and CDRH product jurisdiction officers.** This venue provides for an open discussion of, and progress report on, RFDs and other jurisdictional decisions pending or made in the Centers, and enhances the timeliness, consistency, and clarity of jurisdictional decisions across FDA.
- **Responded to internal and external stakeholder inquiries by providing advice, guidance, and clarification on a variety of informal requests related to the assignment of combination products.** In addition to OCP's review and response to RFDs submitted by industry, OCP responded to over 150 stakeholder inquiries related to product jurisdiction/assignment, primarily by email and telephone. The areas of inquiry encompassed the assignment process to resolving jurisdictional issues on a wide range of specific combination products. OCP received fewer inquiries about the jurisdictional process for combination products in FY 2006, compared to FY 2005, which is likely related to the steps OCP has taken to improve the transparency of the jurisdictional process. These steps include publication of a final rule defining the PMOA of a combination product; publication of a guidance document to assist stakeholders in understanding the kind of information OCP needs in a RFD to make an appropriate determination; and publication of additional information related to the jurisdiction of combination products, such as jurisdictional updates, jurisdictional determinations, and redacted RFD letters.

Timely and Effective Premarket Review

MDUFMA requires OCP to ensure the timely and effective premarket review of combination products by overseeing the timeliness of reviews and coordinating reviews involving more than one Center. On July 31, 2002, FDA issued an internal document to

provide the policies and procedures for FDA staff to follow when requesting, receiving, handling, processing, and tracking formal consultative and collaborative reviews of combination products, devices, drugs, and biologics. The objectives of this document are to improve intercenter communication on combination products, as well as the timeliness and administrative consistency in the conduct of intercenter consultative and collaborative reviews. This document was formally incorporated into the FDA Staff Manual Guide, Agency Program Procedures, Volume IV in July 2005, and is available on the OCP website at www.fda.gov/oc/combination/consultative.html.

Premarket Review

OCP FY 2006 activities and impacts related to premarket review are as follows:

- **Facilitated the premarket review processes for a variety of combination products presenting complex regulatory issues.** OCP fostered early interactions between industry and FDA to develop clearly delineated regulatory schemes for the development and expeditious review of marketing submissions for combination products. Responding to requests from both industry and FDA review staff, OCP consulted on the unique regulatory issues presented by combination products and facilitated meetings and discussions to ensure continued and consistent communication between sponsors and FDA review staff.
- **Responded to more than 230 contacts from Centers and sponsors relating to premarket review issues.** Approximately 60 percent of the contacts were from external stakeholders, and 40 percent of the contacts were from internal stakeholders. OCP facilitated the premarket review process for combination products via more than 100 telephone calls, 80 emails, and 30 meetings. These activities included a number of specific issues that contribute to ensuring the timely and effective review of combination products. Examples include: clinical studies, co-packaged products, cross labeling, indications for use/intended use, labeling, good manufacturing practices, master files, content and format of marketing applications, number of marketing applications, over-the-counter monograph drugs, product design, regulatory pathways, review processes, separately approved products, test methods, and user fees. The OCP facilitations addressed needs in the following areas: anesthesiology, antimicrobials (including antivirals), cardiology, cryosurgery, dentistry, dermatology, drug delivery, gastroenterology, gene therapy, general surgery products, hematology/blood products, hyperthermia, in-vitro diagnostics, iontophoresis, lock-flush products, metabolic disorders (for example, diabetes), neurology, novel drug delivery systems, obstetrics and gynecology, oncology, ophthalmology, orthopedics, otolaryngology, pharmacogenomics, photodynamic therapy, plastic surgery, pulmonology, radiology, respiratory, tissue engineering, urology, vaccine, and wound healing products.
- **Published a guidance document entitled “Guidance for Industry and FDA Staff: Early Development Considerations for Innovative Combination Products.”** This document provides guidance to industry and FDA staff on developmental considerations for innovative products that combine devices, drugs, and/or biological products. It is intended to provide a context for initial discussions on the type of scientific and technical information that may be necessary for investigational or marketing applications for these combination products. FDA recognizes that innovative

technologies may raise a spectrum of scientific and technical development issues. In large part, these issues are due to combination products increasingly incorporating cutting edge, novel technologies that hold great promise for advancing patient care. Innovative drug, biological product, device combinations have the potential to make treatments safer, more effective, or more convenient or acceptable to patients. During an FDA workshop entitled, "*Innovative Systems for Delivery of Drugs and Biologics: Scientific, Clinical and Regulatory Challenges*," industry and academic stakeholders requested that FDA provide guidance for the development of innovative technology that may challenge existing approaches. This document fulfills the request made at the FDA workshop. It does so by addressing the scientific and technical issues to consider when combining drug, device, and/or biological product constituent parts as a combination product. Furthermore, the document also supplements FDA Center websites that already contain a wide variety of guidance documents for the development and testing of drugs, devices, and biological products. The guidance document is published on the OCP website at www.fda.gov/oc/combinati/innovative.html.

- **Convened and chaired a working group to consider the scientific and regulatory issues for autoinjectors.** Autoinjectors are devices that are intended to be used for the delivery of drugs or biological products. The group is working to clarify the number and types of marketing applications typically needed for the review of autoinjectors.
- **Continued development of possible regulatory pathways for new products intended to be used with another sponsor's already approved product.** This work represents the next step following a public workshop titled "Combination Products and Mutually Conforming Labeling" that OCP held on May 10, 2005, in cooperation with the Drug Information Association (DIA). Numerous public health and legal issues were discussed at the workshop and written comments were submitted to OCP following the workshop. These comments have been reviewed, and OCP has developed a possible approach for considering and resolving cross-labeling issues for stakeholder consideration. OCP is scheduling another venue for public participation on this issue, which is planned for 2007.
- **Participated in various intercenter working groups clarifying issues related to combination products.** The working groups are developing policies and guidances for the development, jurisdiction and assignment, and/or regulatory review of a variety of new technologies and types of combination products. Topics covered by specific working groups in FY 2006 include: antimicrobial coatings, data standards, nanotechnology, drug eluting stents, pharmacogenomics, premarket issues, product labeling, and wound care products.
- **Served as a resource for FDA staff on the appropriate use and interpretation of the combination product categorization algorithm and associated categories.** The categories for combination products are based on the types of regulatory issues the products present, for example, a prefilled drug or biologic delivery system, a device physically combined with a drug or biologic, a co-packaged product or kit, or separate products with mutually conforming labeling. All premarket applications in CBER, CDER, and CDRH are categorized as to whether or not they concern a combination product, and if so, what type.

- **Analyzed monthly reports from CBER, CDER, and CDRH capturing data on the categorization of combination products.** Data on new product applications in CBER, CDER, and CDRH are reviewed to ensure that combination product categories are being accurately assigned. Discrepancies are reported to the Centers for correction to ensure the accuracy of the data reported annually to Congress on the numbers and types of combination products under review, as required by MDUFMA. These data are also used by OCP to monitor the progress of premarket applications for combination products under review by FDA.

Consultative/Collaborative Review Process

OCP FY 2006 activities and impacts related to the consultative/collaborative review process are as follows:

- **Actively monitored the intercenter consultation process on combination products under review to ensure the requesting Center received timely and constructive feedback.** OCP tracked, monitored, and followed up on a total of 335 intercenter consult requests in FY 2006, a 22 percent increase in workload over the prior fiscal year (see the section of this report entitled “Report on FY 2006 OCP Requirements, Timely and Effective Premarket Review” for the consult requests by Center).
- **Provided support to FDA review staff to facilitate the intercenter consultation process for intercenter consults.** Many of the consults required extensive OCP involvement in areas that include clarifying internal operating procedures, roles and responsibilities; identification of consulting divisions and contacts; clarification of due dates and completion status; facilitating access to electronic review documents; clarification of specific review requirements; identification and resolution of barriers to timely completion of consultation requests; and ensuring continued effective performance of the courier service for delivery of combination product regulatory documents to CBER, CDER, and CDRH.
- **Facilitated intercenter communication and procedures for the consult review process and issues relating to specific product areas.** OCP facilitations assisted in the review of a wide range of products. Significant consultations requiring multiple meetings and interactions were undertaken in areas such as anesthesia/pulmonary, growth factors, metered-dose inhalers, pain management, radiology, transcutaneous delivery systems, and wound care. Significant issues relating to the consult review process were facilitated in areas such as eRoom, coordination of premarket GMP inspections, general compliance issues, and the adverse event review process for drug eluting stents.

Consistent and Appropriate Postmarket Regulation

MDUFMA requires OCP to ensure the consistency and appropriateness of postmarket regulation of combination products. OCP FY 2006 activities and impacts related to the consistency of postmarketing regulation are as follows:

- **Published a *Federal Register* notice announcing FDA’s plan to develop a proposed rule for postmarketing safety reporting requirements for combination products.** The proposed rule would clarify the postmarket safety reporting requirements for combination products. The proposed rule would provide a framework for the reporting of adverse events for combination products and specify sponsors’ reporting requirements for each type of combination product. The proposed rule would also clarify the circumstances in which following one set of postmarket safety reporting regulations generally would meet the requirements of another set, and the circumstances in which these requirements would be supplemented with specific reporting provisions applicable to the other constituent part of the combination product. The regulation would ensure the consistency and appropriateness of postmarket safety reporting for combination products while avoiding the need for duplicative reporting requirements. The notice, which is included in the Department of Health and Human Services’ Unified Agenda, was published in the April 24, 2006, *Federal Register* (71 FR 22566) and is available on the OCP website at <http://www.fda.gov/oc/comboination/UnifiedAgendaGMPandAE42406.pdf>.
- **Published a *Federal Register* notice announcing FDA’s plan to develop a proposed rule for current good manufacturing practices (cGMP) for combination products.** The proposed rule would clarify and streamline cGMP requirements for combination products. The proposed rule would also provide a flexible quality management regulatory framework that recognizes that, in most instances, for combination products, a properly implemented quality systems (QS) program under one set of medical product cGMP regulations will meet the requirements of another set (for example, application of cGMPs for finished pharmaceuticals in 21 CFR 210/211 will generally meet the requirements of the device Quality System Regulation in 21 CFR 820). This would allow manufacturers the flexibility to select either the cGMP or Quality System Regulation to apply for the manufacture of their combination product, provided that their system incorporates select, key provisions from the regulations pertaining to the other part of their combination product. It would avoid the need to fully implement both sets of cGMP regulations when manufacturing combination products. The proposed rule is intended to ensure consistency and appropriateness in the regulation of combination products. The notice, which is included in the Department of Health and Human Services’ Unified Agenda, was published in the April 24, 2006, *Federal Register* (71 FR 22566) and is available on the OCP website at <http://www.fda.gov/oc/comboination/UnifiedAgendaGMPandAE42406.pdf>.
- **Convened and chaired a working group to consider postmarketing changes to combination products.** During the postmarketing period, manufacturers often make a variety of changes that may affect the safety and effectiveness of a combination product. The goal of this working group is to consider changes that would necessitate certain types of supplemental applications and approaches for how industry might provide the information.

- **Provided clarification and support to Centers and sponsors to ensure consistent and appropriate postmarket regulation of combination products.** OCP responded to approximately 55 separate postmarket issues concerning the postmarket regulation of combination products. These issues included the application of cGMP and quality systems regulations for inspections of combination products, appropriate mechanisms and manufacturer responsibilities for reporting adverse events, requirements for registration and listing, post-approval changes, labeling revisions, repackaging, and off-label use and promotion.

Effective Resolution of Review Disputes

MDUFMA requires OCP to resolve disputes regarding the timeliness of the premarket review of a combination product. OCP FY 2006 activities and impacts related to the effective resolution of review disputes are as follows:

- **Facilitated the resolution of issues presented informally by sponsors concerning the timeliness of premarket review of combination products.** OCP facilitated communications between sponsors and FDA review staff to identify, clarify, and resolve specific concerns associated with review timeliness. These activities help prevent the need for more formal dispute resolution. OCP received no formal dispute resolution requests in FY 2006.

Additional Activities and Impacts

Additional OCP activities and impacts in FY 2006 are as follows:

- **Advanced FDA's Critical Path to New Medical Products Initiative:**
 - OCP continued to be active in the interagency pharmacogenomics working group. OCP assisted in the analysis of the intercenter regulatory process for pharmacogenomic co-development. One of the challenges for pharmacogenomic co-development is the breadth of regulations and intercenter practices for developing therapeutic and diagnostic products. The goal of the interagency working group is to streamline internal processes and clarify the applicable policies for pharmacogenomic development. OCP is working closely with CDER, CDRH, and other FDA components in this effort.
 - OCP continued to participate in the interagency task force on nanotechnology, as the group prepared for an October 2006 public meeting. FDA expects that many future nanotechnology products will be combination products. Therefore, OCP is providing assistance in development of policy for these innovative products.
- **Conducted 30 presentations to external stakeholders and 8 presentations to FDA staff for education and training purposes, and conducted a variety of other outreach activities.** Stakeholder presentations focused on the assignment and regulation of combination products and discussion of OCP activities, initiatives, proposed regulations, and guidances. OCP also had a highly visible role in chairing a session on

combination products during the FDA Centennial Science Forum. In addition to presentations, OCP met with officials of drug and device regulatory authorities from the European Union, several European Union member states, and Japan, to explain how combination products are regulated in the United States. Internal presentations focused on raising awareness of combination product issues, including the intercenter consultation process; the identification and categorization of combination product applications; jurisdiction issues; and adverse event issues relating to combination products. OCP posts many of their presentations on the OCP website at www.fda.gov/oc/combination/presentations/default.htm.

- **Obtained input from internal and external stakeholders:**
 - Met with trade associations and coalitions representing the drug, device, biological product, and combination product industries. Discussions focused on emerging issues in combination product regulation, the role of OCP, policies and guidances under consideration, monitoring intercenter consults, PMOA, cross-labeling of combination products, streamlining cGMP regulations and requirements, adverse event reporting, clarifying the number of marketing applications for combination products, and future industry needs.
 - Conducted periodic meetings with CBER, CDER, CDRH, and FDA senior executive management to discuss key areas of combination products regulation and to discuss and help ensure support for OCP activities and initiatives.
 - Met with other FDA senior executive management officials, including the Acting Commissioner, to brief them on OCP roles, responsibilities, and ongoing initiatives.
- **Responded to a variety of external inquiries and internal requests for reviews of journal articles, books, and presentations concerning combination product regulation and OCP roles and responsibilities.** Reviewed and provided input on a variety of internal and external articles and reports for publication on the regulation of combination products.
- **Responded to requests for interviews and comments concerning combination product regulation and OCP roles and responsibilities.** Responded to media inquiries from a variety of trade press, technology, and scientific journals and publications seeking information about various aspects of how combination products are regulated.
- **Assisted in the advancement of FDA Bioinformatics Initiatives.** OCP staff participated in several interagency working groups and Commissioner-level review boards with the goal of enhancing electronic safety reporting and electronic regulatory submissions pertaining to combination products.

Report on FY 2006 OCP Requirements

MDUFMA requires OCP to provide an annual performance assessment for combination product applications. This section provides performance information for FY 2006 and updates the FY 2005 performance information in the subsection for “Timely and Effective Premarket Review” for reporting the timeliness in days of the reviews of combination products. Unless otherwise noted, all performance information in this section is as of September 30, 2006. Consistent with the mandated functions of the OCP, data highlighted in this section include:

- Timeliness in days of the assignment of combination products
- Number and types of combination products under review
- Timeliness in days of the reviews of combination products
- Number of premarket reviews of combination products that involved a consulting Center

Prompt Assignment of Combination Products

Requirement – Report the Timeliness in Days of the Assignment of Combination Products

FDA is to assign premarket review responsibility for combination products based on the product's PMOA. By submitting an RFD, a company may obtain a formal FDA determination of a combination product's PMOA and assignment of the lead Center for the product's premarket review and regulation. OCP must make its jurisdictional determination within 60 days of filing the RFD, or the sponsor's recommendation of the Center with primary jurisdiction will become the assigned Center.

Requirement Type	Requirement Time Frame
Request for Designation	60 calendar days

Workload

One request for assignment of a combination product was carried over from FY 2005 (pending and not overdue as of October 1, 2005), and 29 requests for combination products were filed during FY 2006 for a total of 30 requests. This reflects a 43 percent increase in the number of RFDs for combination products compared to the 21 RFDs for combination

Combination Product Assignment Requests	
Primary Center	Number of Product Assignments
CBER	7
CDER	5
CDRH	14
Pending	4
Total Requested	30

products filed as reported in the FY 2005 OCP Performance Report. Of the 30 FY 2006 requests, 7 combination products were assigned to CBER, 5 to CDER, and 14 to CDRH (see table above). The remaining four requests for combination products were pending and not overdue as of September 30, 2006.

Prompt Assignment of Combination Products

Performance

Of the 26 assignments issued, 19 combination products were determined to be drug-device combinations, 5 were device-biologic combinations, 1 was a drug-biologic combination, and 1 was a drug-device-biologic combination (see table below). All (26 of 26) product assignments were issued within the 60-day time frame, with a median assignment time of 36 days. Assignment time is equal to the number of days from receipt of the RFD to the issuance of the assignment letter.

Combination Product Requests for Assignment						
Total Requests for Assignment Submitted⁵	Product Assignments Issued⁶	Product Assignments Pending (not overdue)	Product Assignments Pending (overdue)	Product Assignments (Percent) Within 60 days	Median Product Assignment Time (days)	Range of Product Assignment Time (days)
30	26	4	0	100	36	3 to 56

More detailed FY 2006 RFD performance information, including OCP's review of RFDs for non-combination products, is available at the OCP Internet site <http://www.fda.gov/oc/combination/fy06rfd.html>.

⁵ Includes one RFD that was pending at the beginning of the period.

⁶ Does not include two requests for reconsideration for combination products that were issued within the 15-day time frame provided by 21 CFR 3.8.

Timely and Effective Premarket Review

Requirement – Report the Number and Types of Combination Products Under Review

FDA is to report the number and types of combination products under review. OCP, CBER, CDER, and CDRH developed a process to collect the necessary data and report on the required information enacted in MDUFMA. This process was implemented April 1, 2003.

- CBER's and CDER's data collection systems identify combination product status when applications are submitted for review. Therefore, when reporting the number and types of combination products under review for FY 2006, CBER and CDER included applications FDA received in FY 2006.
- As of April 1, 2006, CDRH's data collection system began recording the combination product status when applications are submitted for review. Because CDRH's new method for collecting data was implemented half way through the fiscal year, CDRH continued to report the combination product status at application close-out (when review decisions were made) for FY 2006. In FY 2007, CDRH will report the combination product status when applications are submitted for review.

Timely and Effective Premarket Review

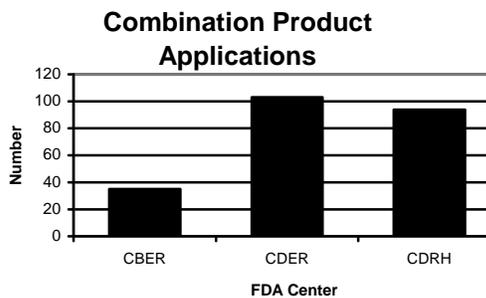
The table below reflects the number of original applications for NDAs, BLAs, PMAs, 510(k)s, INDs, IDEs, and HDEs initially classified into one of nine categories of combination products in FY 2006.⁷ FDA initially categorized 231 original applications under review as combination products.

Number and Types of Combination Products										
Application Type	Combination Product Category									TOTALS
	1	2	3	4	5	6	7	8	9	
Original NDAs	1	11	--	--	--	--	--	--	--	12
Original BLAs	1	--	1	--	--	--	--	--	--	2
Original PMAs	--	--	--	2	1	--	1	--	--	4
Original 510(k)s	--	--	--	58	7	--	2	1	5	73
Original INDs	--	59	17	1	8	13	3	17	4	122
Original IDEs	1	--	--	5	10	--	1	--	1	18
Original HDEs	--	--	--	--	--	--	--	--	--	--
TOTALS	3	70	18	66	26	13	7	18	10	231

<p>APPLICATION KEY:</p> <p>NDAs = New Drug Applications BLAs = Biologics License Applications PMAs = Premarket Approval Applications 510(k)s = Premarket Notifications INDs = Investigational New Drug Applications IDEs = Investigational Device Exemptions HDEs = Humanitarian Device Exemptions</p>	<p>COMBINATION PRODUCT KEY:</p> <p>1 = convenience kit or co-package 2 = prefilled drug delivery device/system 3 = prefilled biologic delivery device/system 4 = device coated/impregnated/otherwise combined with drug 5 = device coated or otherwise combined with biologic 6 = drug/biologic combination 7 = separate products requiring mutually conforming labeling 8 = possible combination based on mutually conforming labeling of separate products 9 = other type of combination product</p>
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Workload

Of the 231 original combination product applications, CBER received and categorized 35 applications as combination products; CDER received and categorized 102 applications as combination products; and CDRH categorized 94 applications as combination products.



⁷ The "Number and Types of Combination Products" categorized for FY 2005 is updated in Appendix A.

Timely and Effective Premarket Review

Requirement – Report the Timeliness in Days of the Reviews of Combination Products

FDA is to report the timeliness in days of the reviews of combination products. The table below summarizes the review type and review performance target for original NDAs, BLAs, PMAs, and 510(k)s. PDUFA and MDUFMA established review performance goals for many types of drug, device, and biological product premarket applications.⁸ These goals reflect current expectations about the portion of premarket applications that will be reviewed within a specified time frame. Performance goals apply to only a portion of all applications of a certain type, and they do not require that every application be reviewed in accordance with the applicable time frame.

User Fee Act	Original Application Type	Review Type	Review Within ⁹	Performance Level	
				FY 2005	FY 2006
PDUFA	NDAs	Priority	6 months	90%	90%
		Standard	10 months	90%	90%
	BLAs	Priority	6 months	90%	90%
		Standard	10 months	90%	90%
MDUFMA	Expedited PMAs	FDA decision ¹⁰	300 days	70%	80%
	PMAs	FDA decision ¹⁰	320 days	--	80%
	510(k)s	“Substantially equivalent” (SE) or “not substantially equivalent” (NSE) decision ¹⁰	90 days	75%	75%
	BLAs	Priority	6 months	--	75%
		Standard	10 months	--	75%

The FDA review performance information for CBER, CDER, and CDRH are based on a fiscal year receipt cohort. This methodology calculates performance information for applications for the fiscal year FDA received them, regardless of when FDA acted on or approved the submissions. This section updates FDA’s review performance on the FY 2005 combination product application submissions and presents FDA’s review performance on the FY 2006 combination product application submissions through September 30, 2006.

⁸ Only MDUFMA decision goals for expedited and original PMAs, 510(k)s, and BLAs are referenced in this report.

⁹ Some product review goals, such as NDAs, are determined by months. Due to the fluctuation in days of individual months (28 to 31), 10 months ranges from 303 days (February 1 to December 1) to 306 days (March 15 to January 15) and 6 months ranges from 182 days (February 15 to August 15) to 184 days (July 15 to January 15).

¹⁰ The decision goal is a goal on a final action, ending the review process. FDA decisions for PMAs are approval, approvable, approvable pending GMP inspection, not approvable, or denial.

Timely and Effective Premarket Review

Performance – CBER-led or CDER-led Combination Products

FY 2005 Submissions

Fourteen FY 2005 PDUFA submissions identified as CBER-led or CDER-led combination products were reviewed and acted on as of September 30, 2006. These actions included 2 priority and 10 standard NDA combination product submissions and 1 priority and 1 standard BLA combination product submissions (see table below).

PDUFA Original Application Type	Review Type	Review Within	Reviewed and Acted On ¹¹	Number on Time ¹²	Median or Actual Review Time ¹³ (days)	Range of Review Time (days)	
						Min	Max
NDAs	Priority	6 months	2	2	225	182	267
	Standard	10 months	10	10	303	293	396
BLAs	Priority	6 months	1	1	266	266	266
	Standard	10 months	1	1	304	304	304

FY 2006 Submissions

Two FY 2006 PDUFA submissions identified as CBER-led or CDER-led combination products were reviewed and acted on as of September 30, 2006. These actions included 1 standard NDA and 1 priority BLA combination product submissions (see table below). Additional NDAs and BLAs were under review, with decisions pending. FDA will update the FY 2006 submission data in the FY 2007 OCP Performance Report.

PDUFA Original Application Type	Review Type	Review Within	Reviewed and Acted On ¹¹	Number on Time	Median or Actual Review Time ¹³ (days)	Range of Review Time (days)	
						Min	Max
NDAs	Priority	6 months	0	--	--	--	--
	Standard	10 months	1	1	302	302	302
BLAs	Priority	6 months	1	1	183	183	183
	Standard	10 months	0	--	--	--	--

¹¹ The number of combination product submissions is a small subset of the total number of submissions received by FDA.

¹² Major amendments were received within 3 months of the action due date, which extended the review time frames by 3 months for the following combination product submissions: 1 of 2 priority NDAs, the 1 of 1 priority BLA, and 3 of 10 standard NDAs.

¹³ Median review time is based on FDA first cycle review performance. Actual review time was used when only one action was measured.

Timely and Effective Premarket Review

Performance – CBER-led or CDRH-led Combination Products

FY 2005 Submissions

Fifty-nine FY 2005 MDUFMA submissions identified as CBER-led or CDRH-led combination products had FDA decisions reached as of September 30, 2006. These decisions included 1 expedited PMA, 1 original PMA, and 57 premarket notification [510(k)] combination product submissions (see table below).

MDUFMA Original Application Type ¹⁴	Review Type	Review Within	Decisions Reached ¹¹	Number on Time ¹⁵	Median or Actual Review Time ¹⁶ (days)	Range of Review Time (days)	
						Min	Max
Expedited PMAs	FDA decision	300 days	1	1	290	290	290
PMAs	FDA decision	320 days	1	1	264	264	264
510(k)s	SE or NSE decision	90 days	57	45	69	16	194

FY 2006 Submissions

Sixty-six FY 2006 MDUFMA submissions identified as CBER-led or CDRH-led combination products had FDA decisions reached as of September 30, 2006. All decisions made were on 510(k) submissions, which have shorter review times (see table below). Additional PMA and 510(k) combination product submissions were under review, with decisions pending. FDA will update the FY 2006 submissions table in the FY 2007 OCP Performance Report.

MDUFMA Original Application Type ¹⁴	Review Type	Review Within	Decisions Reached ¹¹	Number on Time ¹⁵	Median or Actual Review Time ¹⁶ (days)	Range of Review Time (days)	
						Min	Max
Expedited PMAs	FDA decision	300 days	0	--	--	--	--
PMAs	FDA decision	320 days	0	--	--	--	--
510(k)s	SE or NSE decision	90 days	66	60	57	10	138

¹⁴ FDA did not identify any MDUFMA-related BLA combination product submissions for FY 2005 and FY 2006.

¹⁵ Performance goals apply to only a portion of applications of a certain type, and they do not require that every application be reviewed in accordance with the applicable time frame.

¹⁶ Median review time is based on total FDA decision review time. Actual review time was used when only one action was measured.

Timely and Effective Premarket Review

Requirement – Report the Number of Premarket Reviews of Combination Products That Involved a Consulting Center

FDA is to report the number of premarket reviews of combination products that involved a consulting Center. The table below reflects the Intercenter Requests for Consultative or Collaborative Review forms received and monitored by OCP during FY 2006.¹⁷ As the primary assigned Center, CBER requested 40 intercenter consultations (7 consultations with CDER, 33 consultations with CDRH); CDER requested 64 intercenter consultations (2 with CBER and 62 with CDRH); and CDRH requested 231 intercenter consultations (10 with CBER, 221 with CDER).

		Consulting Center			Number of Consults
		CBER	CDER	CDRH	
Primary Assigned Center	CBER	--	7	33	40
	CDER	2	--	62	64
	CDRH	10	221	--	231
Totals		12	228	95	335

The monitored Intercenter Requests for Consultative or Collaborative Review forms represent a 22 percent increase over the 275 consults reported in the FY 2005 OCP Performance Report, and are indicative of the growing number of premarket reviews of combination products that involved a consulting Center.

¹⁷ Some applications were associated with multiple consulting requests. Additionally, because these consulting requests are associated with any combination product under review for which consultative or collaborative review is needed, regardless of the date of FDA receipt of the application, the number of requests is not directly comparable to the number of combination product applications received during FY 2006, as reported in the previous section.

Effective Resolution of Review Disputes

Requirement – Report the Timeliness in Days of Dispute Resolutions Regarding Combination Products

FDA is to report the timeliness in days of dispute resolutions regarding combination products. No formal requests to resolve a dispute regarding the timeliness of a combination product review were received during FY 2006. While this was the fourth straight year no formal requests were received, the “Activities and Impacts for FY 2006, Premarket Review” section of this report provides examples of informal facilitation and resolution of issues related to premarket review. Informal activities help prevent the need for formal dispute resolution.

APPENDIX A: Timely and Effective Premarket Review – Updated FY 2005 Data

In FY 2005, FDA categorized 273 original applications under review as combination products. The table below reflects the number of original applications classified into one of nine combination product categories for original NDAs, BLAs, PMAs, 510(k)s, INDs, IDEs, and HDEs.

Number and Types of Combination Products										
Application Type	Combination Product Category									TOTALS
	1	2	3	4	5	6	7	8	9	
Original NDAs	2	9	--	--	--	--	1	--	--	12
Original BLAs	1	--	1	--	--	--	--	--	--	2
Original PMAs	--	--	--	2	--	--	--	--	--	2
Original 510(k)s	5	--	--	55	8	--	4	--	3	75
Original INDs	2	48	12	3	5	12	17	56	1	156
Original IDEs	1	--	--	18	5	--	1	1	--	26
Original HDEs	--	--	--	--	--	--	--	--	--	--
TOTALS	11	57	13	78	18	12	23	57	4	273

<p>APPLICATION KEY:</p> <p>NDAs = New Drug Applications BLAs = Biologics License Applications PMAs = Premarket Approval Applications 510(k)s = Premarket Notifications INDs = Investigational New Drug Applications IDEs = Investigational Device Exemptions HDEs = Humanitarian Device Exemptions</p>	<p>COMBINATION PRODUCT KEY:</p> <p>1 = convenience kit or co-package 2 = prefilled drug delivery device/system 3 = prefilled biologic delivery device/system 4 = device coated/impregnated/otherwise combined with drug 5 = device coated or otherwise combined with biologic 6 = drug/biologic combination 7 = separate products requiring mutually conforming labeling 8 = possible combination based on mutually conforming labeling of separate products 9 = other type of combination product</p>
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Of the 273 original combination product applications, CBER received and categorized as combination products 31 applications; CDER received and categorized as combination products 139 applications; and CDRH categorized 103 applications, which were reviewed and acted on as of September 30, 2006.

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APPENDIX B: Summary of Footnotes

¹ These activities are in addition to a wide range of OCP activities associated with its review of and response to Requests for Designation.

² This is in accordance with section 503(g)(1) of the Act (21 U.S.C. 353(g)(1)).

³ The RFD process, including the information required in a RFD submission, is outlined in 21 CFR Part 3.

⁴ This is by operation of section 563 of the Act (21 U.S.C. 360bbb-2).

⁵ Includes one RFD that was pending at the beginning of the period.

⁶ Does not include two requests for reconsideration for combination products that were issued within the 15-day time frame provided by 21 CFR 3.8.

⁷ The “Number and Types of Combination Products” categorized for FY 2005 is updated in Appendix A.

⁸ Only MDUFMA decision goals for expedited and original PMAs, 510(k)s, and BLAs are referenced in this report.

⁹ Some product review goals, such as NDAs, are determined by months. Due to the fluctuation in days of individual months (28 to 31), 10 months ranges from 303 days (February 1 to December 1) to 306 days (March 15 to January 15) and 6 months ranges from 182 days (February 15 to August 15) to 184 days (July 15 to January 15).

¹⁰ The decision goal is a goal on a final action, ending the review process. FDA decisions for PMAs are approval, approvable, approvable pending GMP inspection, not approvable, or denial.

¹¹ The number of combination product submissions is a small subset of the total number of submissions received by FDA.

¹² Major amendments were received within 3 months of the action due date, which extended the review time frames by 3 months for the following combination product submissions: 1 of 2 priority NDAs, the 1 of 1 priority BLA, and 3 of 10 standard NDAs.

¹³ Median review time is based on FDA first cycle review performance. Actual review time was used when only one action was measured.

¹⁴ FDA did not identify any MDUFMA-related BLA combination product submissions for FY 2005 and FY 2006.

¹⁵ Performance goals apply to only a portion of applications of a certain type, and they do not require that every application be reviewed in accordance with the applicable time frame.

¹⁶ Median review time is based on total FDA decision review time. Actual review time was used when only one action was measured.

¹⁷ Some applications were associated with multiple consulting requests. Additionally, because these consulting requests are associated with any combination product under review for which consultative or collaborative review is needed, regardless of the date of FDA receipt of the application, the number of requests is not directly comparable to the number of combination product applications received during FY 2006, as reported in the previous section.



**Department of Health and Human Services
Food and Drug Administration**



This report was prepared by FDA's Office of Combination Products in collaboration with the Office of Planning, Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and the Center for Devices and Radiological Health. For information on obtaining additional copies contact:

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