FY 2010

PERFORMANCE REPORT TO CONGRESS

for the

Office of Combination Products

as required by the

Medical Device User Fee and Modernization Act of 2002

Food and Drug Administration
Department of Health and Human Services

Commissioner's Report

I am pleased to submit the Food and Drug Administration's (FDA's) Fiscal Year (FY) 2010 Annual Report to Congress for the Office of Combination Products (OCP). This report includes the seventh full year of data since OCP was established as mandated by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA I), enacted on October 26, 2002.

Combination products are therapeutic and diagnostic products that combine drugs, devices, and/or biological products. Technological advances continue to merge product types and blur the historical lines of separation between FDA's human medical product centers, which are made up of the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH). Because combination products involve components that would normally be regulated under different types of regulatory authorities, and frequently by different FDA Centers, they raise regulatory, policy, and review management challenges. Differences in regulatory pathways for each component can impact the regulatory processes for all aspects of product development and management, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, user fees, and post-approval modifications.

OCP continues to enhance the transparency and predictability of the combination product lead Center assignment and review process. In this regard, OCP facilitates interactions between industry and FDA to clearly delineate regulatory paths, continues to monitor and adjust processes to ensure timely and effective review, and continues to ensure the consistent and appropriate postmarket regulation of combination products. In addition to combination products, OCP also has classification and assignment responsibilities for non-combination drug, device, and biologic products.

Combination products are likely to become more complicated as new technologies emerge and existing technologies mature. Therefore, OCP will continue to focus on the most important issues relating to the regulation of combination products. OCP is committed to actively assisting industry and FDA staff in understanding this complex regulatory area. A major OCP accomplishment in FY 2010 was the issuance of the final guidance *New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products* as required in the Medical Device User Fee Amendments of 2007 (MDUFA II) commitment letter to Congress.

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

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

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Executive Summary

FDA established OCP on December 24, 2002, as required by MDUFMA I. 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 and covers activities and accomplishments during FY 2010, the period from October 1, 2009 through September 30, 2010. OCP activities for FY 2010 highlighted in this report include the following:

- **Prompt Assignment of Combination Products**. In FY 2010, OCP continued to clarify the jurisdictional assignment of combination products and to provide prompt Request for Designation (RFD) decisions. OCP issued 32 combination product RFD assignments with 100 percent of these assignments meeting the 60-day statutory decision time requirement. For the classification and jurisdictional assignment of non-combination products, OCP issued 12 RFD assignments with 100 percent of these assignments meeting the 60-day statutory decision time requirement. OCP also provided timely informal jurisdictional assistance for approximately 303 separate issues, representing an 18 percent increase in the number of informal inquiries from FY 2009.

- **Timely and Effective Premarket Review**. In FY 2010, OCP published the final guidance entitled *New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products*. The final guidance is available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM195951.pdf. OCP also continued to make significant contributions to the premarket review of combination products by responding to 551 inquiries from Centers and sponsors. The number of issues to which OCP responded increased 30 percent in FY 2010 from FY 2009. Other OCP activities relating to premarket review included chairing and/or participating in a number of working groups examining issues clarifying interpretive standards, addressing challenging categories of products, and continuing to develop guidance documents on how to determine whether a product is a drug, device, biological product, or combination product.

- **Combination Product Review.** FDA received 311 original premarket applications for combination products in FY 2010. This amount represents an 11 percent decrease from 350 original applications for combination products received in FY 2009.[1]

[1] FY 2009 numbers were changed to reflect updates to data presented in the FY 2009 OCP Performance Report. The updated data for FY 2009 is located in Appendix A.

Additionally, the number of intercenter consulting reviews increased to 466 for FY 2010 from 455 in FY 2009. This represents a 2 percent increase in intercenter consults. Examples of approved combination products can be found at the OCP Web site: http://www.fda.gov/CombinationProducts/default.htm.

- **Consistent and Appropriate Postmarket Regulation.** OCP chaired a working group to review comments received in response to two proposed rules and to develop the final rules. These rules will clarify which current good manufacturing practices (cGMPs) apply for combination products and the postmarket safety reporting requirements for combination products. OCP also worked with the FDA Centers to resolve postmarket safety issues pertaining to specific combination products.

- **Additional Activities and Accomplishments**. OCP continued to conduct external outreach activities through a variety of educational and informational presentations to national and international audiences. 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. OCP also conducted activities that advanced the development and review of innovative products. Other activities included participating in efforts to improve FDA electronic databases, nanotechnology initiatives, and biosimilar activities.

Throughout FY 2010, OCP strived to ensure the prompt assignment of medical products to Centers, the timely and effective premarket review, and the consistent and appropriate postmarket regulation of combination 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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Overview of Combination Products

On October 26, 2002, Congress enacted MDUFMA I. Among other things, MDUFMA I required FDA to establish an office "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. In response, FDA established OCP within the Office of the Commissioner. Information about OCP, including the authorizing text of MDUFMA I, can be found at the OCP Web site: http://www.fda.gov/CombinationProducts/default.htm.

MDUFMA I also required FDA to submit an annual report to Congress on the activities and impact of OCP. This document fulfills this requirement for FY 2010. In reauthorizing medical device user fees under MDUFA II, no new reporting requirements were included on the activities and impact of OCP.

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

(1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that is 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; or,

(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.

Combination products have the potential to provide enhanced therapeutic advantages compared to single entity devices, drugs, and biologics, and incorporate cutting-edge, novel technologies that hold great promise for advancing patient care. Combination

products may include drug-delivery systems, gene therapy systems, personalized medicine drug-device combinations, biological-device combinations, nanotechnology, and other innovative products for diagnostic and therapeutic treatments of cardiovascular, metabolic, oncologic, and other disorders.

Mandated Functions of OCP

MDUFMA I 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 the three product Centers – CBER, CDER, or CDRH – to which they are assigned by OCP. Specifically, the statute (section 503(g)(4)(B-F) of the Federal Food, Drug, and Cosmetic Act) 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 guidances and regulations to clarify the regulation of combination products.

In addition, OCP has responsibility for FDA action on all RFDs submitted by industry in accordance with 21 CFR Part 3. This responsibility 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.

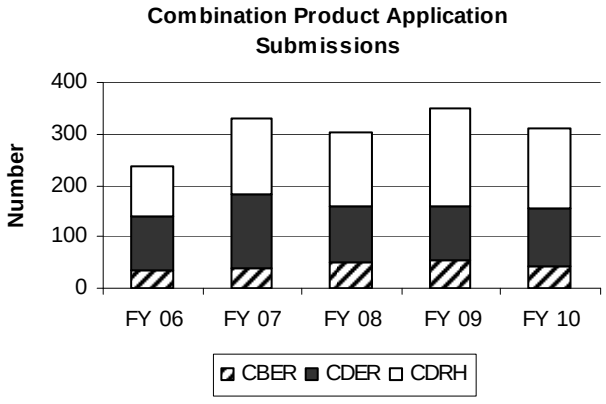
OCP Organizational Structure

As of September 30, 2010, OCP was staffed by eight permanent full-time positions and one temporary position. These positions included the Director, Deputy Director, an Associate Director for Policy/Product Classification, a Product Jurisdiction Assignment Officer, two Scientific Reviewers, one Medical Officer, one Management Analyst, and one temporary scientific reviewer position. The office is located on the FDA White Oak Campus, Building 32, 10903 New Hampshire Avenue, Silver Spring, MD 20993, telephone: (301) 796-8930, fax: (301) 847-8619, email: combination@fda.gov.

Five-Year Trends in Combination Product Submissions and Requests

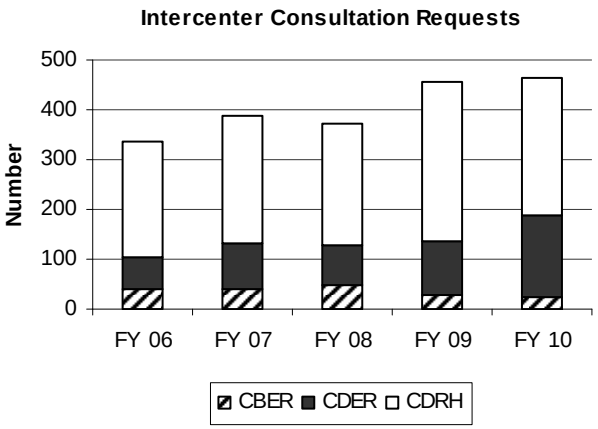
Since combination products involve components (biologics, drugs, and/or devices) that would normally be regulated under different types of regulatory authorities, and frequently by different FDA Centers, they also raise challenging regulatory, policy, and review management issues. The differences in regulatory pathways for each component can impact 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.

The number of combination products submitted for review in FY 2010 decreased from FY 2009 but remained greater than the FY 2006 and FY 2008 levels (see corresponding graph). The number of combination products submitted for review decreased by 11 percent from 350 in FY 2009 to 311 in FY 2010. A decrease in application submissions for the review of combination products occurred for CBER and CDRH in FY 2010 (from 53 to 44 and from 190 to 155, respectively) while the number for CDER increased from 107 to 112.[2]

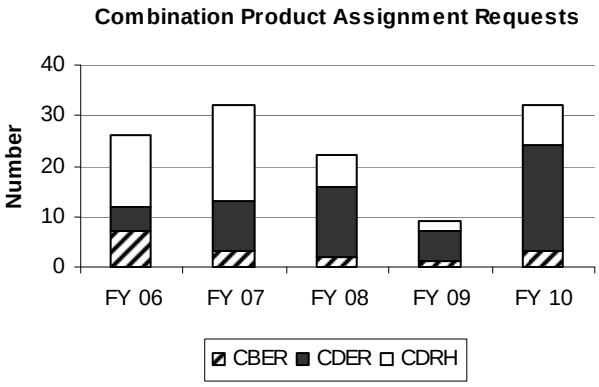


[2] FY 2009 numbers were changed to reflect updates to data presented in the FY 2009 OCP Performance Report. The updated data for FY 2009 is located in Appendix A.

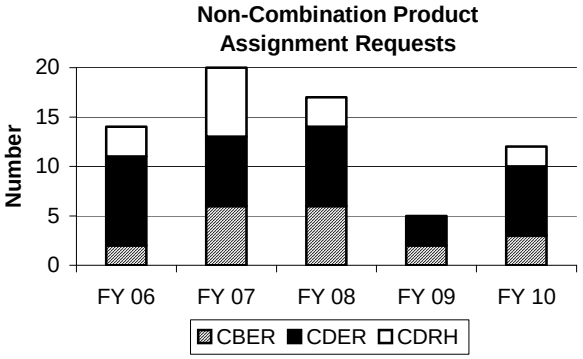
The number of intercenter consult requests increased in FY 2010 to a 5-year high. The number of intercenter consultation requests on combination products increased for two consecutive years (FY 2009 and FY 2010). While the number of requests from CDER increased in FY 2010 (from 107 to 162), the number of requests from CDRH (from 320 to 279) and CBER (from 28 to 25) decreased during the same period.



The number of formal combination product assignment requests issued increased in FY 2010, sharing the 5-year high with FY 2007. The number of assignment requests issued increased by 256 percent, from 9 in FY 2009 to 32 in FY 2010, after decreasing for two consecutive years (FY 2008 and FY 2009) (see corresponding graph). Assignment requests issued increased for CBER (from 1 to 3), CDER (from 6 to 21), and CDRH (2 to 8).



The number of formal product assignment requests for non-combination products increased in FY 2010 after decreasing for two consecutive years (FY 2008 and FY 2009). The number of non-combination product assignment requests issued increased by 140 percent from 5 in FY 2009 to 12 in FY 2010 (see corresponding graph). Assignments increased for CBER (from 2 to 3), CDER (from 3 to 7), and CDRH (from 0 to 2).



Report on FY 2010 OCP Activities and Accomplishments

This section includes FY 2010 activities and accomplishments of OCP in the assignment of combination products and in coordinating the review and regulation of combination products. OCP documented 641 activities in FY 2010.[3] These documented records included 515 activities conducted with stakeholders external to FDA and 148 with internal stakeholders. As provided further in this section, the topics of the activities included jurisdiction/classification assignments (303 activities); premarket review issues (551 activities); and postmarket regulation issues (60 activities). Consistent with the mandated functions of OCP, information in this section presents OCP activities related to:

- 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, 2010.

Prompt 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). 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. 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. In addition, companies and Centers often informally request assistance from OCP in working out jurisdictional issues not raised in an RFD submission.

OCP FY 2010 accomplishments related to the assignment of combination products included:

- **Issuing all required assignments within the 60 days.** RFD performance data for the assignment of combination and non-combination products in FY 2010 are presented in the next section of this report.

[3] These activities are in addition to a wide range of OCP activities associated with its monitoring of intercenter consults and its review of and response to RFD submissions. Additionally, some of the total reported activities may have involved more than one type of activity (e.g., premarket review issues and postmarket regulation issues or internal and external stakeholders) and may be represented in multiple types of activities.

- **Responding to 303 stakeholder inquiries related to product classification and jurisdiction assignments, primarily by e-mail and telephone**. This represents 47 more informal requests for classification and jurisdictional assignment in FY 2010 than during FY 2009, an 18 percent increase in the number of informal inquiries.

- **Chairing an intercenter working group to clarify standards for product classification and prepare guidance on this issue.** Classification and jurisdictional decisions are made based on the statutory definitions of drug, device, biological product, and combination product, which often raise novel interpretive questions. OCP chaired a working group to clarify interpretive standards, address challenging categories of products, and continue to develop guidance documents on how to determine whether a product is a drug, device, biological product, or combination product.

- **Conducting monthly product jurisdiction meetings to enhance the timeliness, consistency, and clarity of jurisdictional decisions across FDA.** OCP continued to facilitate the exchange of information between OCP jurisdictional and assignment specialists; CBER, CDER, and CDRH product jurisdiction officers; and attorneys from the Office of Chief Counsel (OCC). The monthly product jurisdiction meetings provide 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.

Timely and Effective Premarket Review

OCP is required 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. In 2002, FDA established 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. This policy was formally incorporated into the FDA Staff Manual Guide, Agency Program Procedures, Volume IV in July 2005, and is available on the OCP Web site.

Premarket Review Process. OCP facilitates the premarket review processes for combination products having complex regulatory issues. OCP fosters early interactions between industry and FDA to develop clearly delineated regulatory schemes for the development and review of marketing submissions for combination products. Responding to requests from both industry and FDA review staff, OCP consults and provides guidance on unique regulatory issues presented by combination products. OCP also

facilitates and leads or participates in meetings and discussions to ensure continued and consistent communication between sponsors and FDA review staff. OCP FY 2010 accomplishments related to premarket review included:

- **Responding to 551 contacts from Centers and sponsors relating to premarket review issues.** This represents 128 more responses to contacts from Centers and sponsors in FY 2010 than during FY 2009, representing a 30 percent increase in the number of responses. The responses to contacts addressed a number of specific issues that contributed to ensuring the timely and effective review of combination products. OCP facilitations addressed needs in areas such as: drug delivery, *in-vitro* diagnostics, medical imaging, pharmacogenomics, photodynamic therapy, and wound healing products.

- **Issuing Final *Guidance to Industry - New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products (December 2009)* as called for under MDUFA II**. The draft guidance was published on September 30, 2008 with the comment period closing on January 5, 2009. FDA held meetings with imaging industry stakeholders in July 2008 and August 2009. The final guidance is available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM195951.pdf.

- **Continuing development of possible regulatory pathways for new products intended to be used with another sponsor's already approved product.** Subsequent to an OCP public workshop held in FY 2005 entitled, "Combination Products and Mutually Conforming Labeling," and in cooperation with the Drug Information Association, OCP continued to develop clarifications on numerous public health and legal issues that were discussed at the meeting and in written comments submitted to OCP. OCP frequently worked with the Centers and OCC on a specific product to develop approaches to resolve complex legal and public health issues associated with cross-labeling combination product issues. OCP will continue to develop information for stakeholder comment on the regulatory approaches for cross-labeling to ensure safety and effectiveness of differently regulated products. In the interim, some aspects of cross-labeling considerations were included in the draft guidance entitled, *New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products.*

- **Participating in intercenter working groups to clarify issues related to combination products and product jurisdiction.** The intercenter working groups develop policies and technical guidance on topics that include: artificial pancreas, biosimilar products, nanotechnology, premarket issues, product labeling, biologics and tissues, wound care, intrathecal delivery products, and medical gases. OCP participated in intercenter ad-hoc working groups to develop responses to Citizen's Petitions for certain combination products for approval under section 505(b)(2) and section 505(j).

- **Serving as a resource for FDA staff on the appropriate use and interpretation of the combination product categorization algorithm and associated categories.** Categories for combination products are based on the types of regulatory issues the products present such as, 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 they concern a combination product, and if so, what type. OCP continues to interact with the Centers to promote consistency in categorization.

Consultative/Collaborative Review Process. OCP oversees intercenter consults to ensure that review of premarket applications are completed in a timely manner and meet Prescription Drug User Fee Act (PDUFA) and MDUFA II timelines. Specifically, OCP tracks and monitors all ongoing intercenter consult requests; clarifies internal operating procedures, roles, and responsibilities; identifies consulting divisions and contacts; clarifies due dates and completion status; facilitates access to review documents; and responds to industry inquiries. Other areas of OCP involvement, on a less routine basis, include clarifying the impact of goal differences under PDUFA and MDUFA II and resolving barriers to timely completion of consultation requests.

In addition to providing general consult process assistance and facilitating intercenter communication, OCP also provides assistance to the Centers in resolving regulatory and scientific issues relating to specific combination products. The following list represents some product specific groups that OCP provided significant facilitation assistance during FY 2010:

- injector delivery systems (including intrathecal systems)
- medical imaging drugs and devices
- wound care
- traditional products with novel combination uses

The following list illustrates additional areas where OCP provided significant assistance during FY 2010:

- coordination of premarket cGMP inspections
- certificates to foreign governments
- cross-labeling
- electronic submissions
- intercenter compliance consultations
- registration and listing
- Unique Device Identifiers and Standardized Numerical Identification
- regulatory approach for devices that enhance the safety of drug and biological products
- advisory and panel process clarifications for combination products
- risk determination and need for investigational application assessments
- legal status of products imported from outside the United States

OCP FY 2010 accomplishments related to the consultative/collaborative review process included:

- **Actively tracking, monitoring, and following up on a total of 466 intercenter consult requests on combination products under review to ensure the requesting Center received timely and constructive feedback.** Additional information on consult requests by Center are presented in the next section of this report.

Consistent and Appropriate Postmarket Regulation

OCP is required to ensure the consistency and appropriateness of postmarket regulation of combination products. OCP accomplishes this requirement by undertaking a variety of compliance-related and postmarketing activities to help ensure the safety and quality of combination products. The compliance-related and postmarketing activities include coordinating FDA responses with the Centers to postmarket safety reports and providing guidance, facilitating, and leading meetings between industry and the Centers on cGMP requirements. Other compliance-related and postmarketing activities include providing support to FDA field inspectors for products seized at ports of U.S. entry to stop illegal products from entering the country, responding to product defect issues, providing guidance on enforcement issues relating to the Prescription Drug Marketing Act and import requirements, and providing warning letter guidance. OCP FY 2010 accomplishments related to the consistency of postmarketing regulation included:

- **Developing a final rule on the cGMP requirements for combination products.** OCP published a proposed rule in FY 2009 to clarify and codify the cGMP requirements for combination products. In FY 2010, OCP chaired a working group to review comments received and develop a final rule and associated guidance. The rule is intended to ensure consistency and appropriateness in the regulation of combination products, while providing a flexible quality management regulatory framework. The quality management regulatory framework for combination products is based on the premise that, in most instances, a properly implemented quality system program under either the drug cGMP set of regulations at 21 CFR 210 and 211 or the device quality system set of regulations at 21 CFR 820 will generally satisfy the requirements of both sets of regulations. The proposed rule would, therefore, allow manufacturers the flexibility to implement either the drug cGMPs or device quality system regulations for the manufacture of their combination product, provided that their quality system incorporates select, key provisions from the other of these two sets of regulations. Manufacturers also would continue to be required to comply with the cGMP regulations for biologics and for human cells, tissues, and cellular and

tissue-based products (HCT/Ps) if their combination products include biologics or HCT/Ps. The proposed rule is available at: http://edocket.access.gpo.gov/2009/pdf/E9-22850.pdf.

- **Developing a final rule on postmarketing safety reporting requirements for combination products.** OCP published a proposed rule in FY 2009 to clarify and codify the postmarket safety reporting requirements for combination products. During FY 2010, OCP chaired a working group to review comments received and prepare a final rule and associated guidance. The rule would provide a framework for the reporting of adverse events for combination products and specifies sponsors' reporting requirements for each type of combination product. FDA believes that the simplest and most straightforward way to ensure that combination products are regulated consistently is by continuing to require reporters to comply with the requirements for postmarketing safety reporting associated with the application used to approve or clear their combination product, as long as specified provisions particular to each different set of regulations are complied with by the reporter. The proposed rule is available at: http://edocket.access.gpo.gov/2009/pdf/E9-23519.pdf.

- **Evaluating FDA-wide policy on combination product registration and listing.** OCP chaired a working group on combination product registration and listing to clarify current policies and to consider whether adjustments should be made to that policy to further enhance product tracking and postmarket regulation, including adverse event response.

- **Facilitating/coordinating intercenter analysis of postmarket safety signals for combination products or related articles.** Safety signals for combination products are submitted to CBER, CDER, and CDRH. To promote consistency in the evaluation in some instances, OCP provided coordination or clarification of regulatory issues to facilitate resolution of the postmarket safety issues. Some issues resulted in product specific regulatory action or public health alerts as appropriate.

- **Providing clarification and support to 60 separate postmarket issues to ensure consistent and appropriate postmarket regulation of combination products.** The postmarket-related issues included the application of cGMPs and quality system regulations for inspections of combination products, appropriate mechanisms and manufacturer responsibilities for reporting adverse events, requirements for registration and listing, post-approval changes, import-export issues, labeling revisions, repackaging, off-label use and promotion, postmarket studies, and safety reporting. OCP also provided product-specific recommendations on the type of submission for postmarket changes being made to a constituent part(s) of a combination product.

Effective Resolution of Review Disputes

FY 2010 was the eighth straight year that FDA received no formal dispute resolution requests. When requests are received, OCP is required to resolve disputes regarding the timeliness of the premarket review of a combination product. OCP facilitates communications between sponsors and FDA review staffs to identify, clarify, and resolve specific concerns associated with review timeliness. The facilitation of issues helps prevent the need for more formal dispute resolution.

Additional Activities and Accomplishments

In addition to the required functions noted above, OCP actively pursues strategies intended to further program objectives internally and externally. While not exhaustive of all of OCP's supplemental activities, the information below highlights additional FY 2010 OCP accomplishments in two key areas:

- External Outreach
- Regulatory Initiatives

External Outreach. OCP conducts outreach activities to share information on FDA assignment and regulation of combination products by meeting with trade associations and coalitions (e.g., Combination Products Coalition and Advanced Medical Technology Association) representing the drug, device, biological product, and combination product industries. Discussions focus 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 in focused areas such as, medical imaging, diabetes, diagnostic products, and novel technologies. Examples of FY 2010 outreach activities included:

- **Conducting 28 presentations and outreach activities to national and international audiences.** OCP participated in outreach activities at 8 international venues/events such as, the Irish Medical Devices Association Global Access 2010 Conference (Limerick, Ireland) and at 20 outreach activities and events across the United States, including the Biotechnology Industry Organization International Convention (Chicago, IL), Regulatory Affairs Professional Society interactive sessions on the proposed cGMP and postmarketing safety rules for combination products (Washington, DC), and The Food and Drug Law Institute Annual Conference (Washington, DC).

- **Developing a proposal for coordinated activity on combination products and other international regulatory activities.** In 2010, OCP participated in an ad hoc meeting with representatives of other components of FDA, and regulators from Australia, Canada, the European Community, and Japan. The purpose of the meeting was to develop a draft proposal to heads of agencies regarding potential areas for the Irish Medicines Board and the Novel Products Task Force of the European Medicines Agency to discuss opportunities for coordination and collaboration in regard to regulation of combination products.

Regulatory Initiatives. OCP activities include efforts to assist in advancing initiatives important to and affecting the regulation of combination products. Examples of regulatory activities pursued in FY 2010 included:

- **Continuing to advance new medical product initiatives.** OCP assisted in defining the regulatory path for novel technology diagnostics and biomarkers under review for use with drug or biological products. OCP also continued to address new emerging nanotechnology products. FDA expects that many future nanotechnology products will be combination products.
- **Actively participating in the FDA Enterprise Initiatives and the development of requirements on drug and device registration and listing.** OCP continues to serve as liaison to several FDA-wide electronic database initiatives with the goal of enhancing the infrastructure necessary to facilitate the safety and effectiveness of combination products and development of FDA-wide medical product databases applicable to combination products. Specifically, these activities covered the system design for postmarket adverse event safety reporting, consistency of electronic regulatory submissions pertaining to combination products, and the infrastructure for ensuring product quality and appropriate registration and listing.
- **Participating in FDA's Nanotechnology Task Force and working groups to address regulation of "biosimilars."** Two major areas of regulatory interest for FDA are products that include nanoscale materials and issues relating to implementing the recently enacted Biologics Price Competition and Innovation Act of 2009 (BPCI). OCP continues to participate in the FDA Nanotechnology Task Force, which addresses various premarket and postmarket issues for products containing nanomaterials. Specifically, OCP staff participated in the development of guidance on regulatory issues for nanotechnology products. In FY 2010, OCP also participated in newly created working groups to address product classification and related issues in relation to the BPCI.

Report on FY 2010 OCP Requirements

OCP is required to provide an annual performance assessment for combination product applications. This section provides performance information for FY 2010 and updates the FY 2009 performance information in the subsection for "Timely and Effective Premarket Review" for reporting the timeliness in days of the reviews of combination products. Consistent with the mandated functions of 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
- Timeliness in days of dispute resolutions regarding combination products

Unless otherwise noted, all performance information in this section is as of September 30, 2010.

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. As part of OCP's review of an RFD submission, a product may be determined to be a non-combination product and classified as either a biologic, drug, or device.

OCP also must make classification determinations for non-combination RFD submissions. As with combination product jurisdictional determinations, non-combination product classification determinations must be made within 60 days of the filing of the RFD.

Requirement Type	Requirement Time Frame
Request for Designation	60 calendar days

Workload

Seven requests for assignment of products were carried over from FY 2009 (pending and not overdue as of October 1, 2009). An additional 45 requests for product assignments were filed during FY 2010. Of the 52 potential assignment requests in FY 2010, 32 were identified as combination products and 12 were identified as non-combination products (see table to the right). Three assignment requests were withdrawn by the sponsor prior to issuance of an FDA decision. Five requests for assignment were carried over to FY 2011 (pending and not overdue assignment as of October 1, 2010).

Requests for Designation Center Assignments		
Primary Center	Number of Product Assignments*	
	Combination Products	Non-Combination Products
CBER	3	3
CDER	21	7
CDRH	8	2
Total Issued	32	12

* Workload also included 44 RFD submissions that were reviewed by OCP and had insufficient information for filing.

Requests for Designation					
FY 2009 Carried Over	FY 2010 Filed	FY 2010 Potential Assignment Requests	Requests for Designation Assigned	Requests for Designation Withdrawn	FY 2010 Carried Over
7*	45	52	44	3	5

* One of the pending RFDs was withdrawn by the sponsor prior to a decision being issued.

Prompt Assignment of Combination Products

Performance

In FY 2010, 44 total combination and non-combination product assignments were issued, all within the 60-day time frame (see table below). Almost three-fourths (32 of 44) of product assignment requests were determined to be combination products. The combination product assignments had a median product assignment time of 58 days. The remaining (12 of 44) product assignment requests were determined to be non-combination product assignments with a median product assignment time of 60 days.

Determination	Product Assignments Issued	Product Assignments (Number) Within 60 days	Product Assignments (Percent) Within 60 days	Median Product Assignment Time (Days)	Range of Product Assignment Time (Days)
Combination Products*****	32	32	100%	58	21 to 60
Non-Combination Products†	12	12	100%	60	48 to 60

* Includes four RFDs that were pending at the beginning of FY 2010. Does not include four requests for reconsideration for combination products that were issued within the 15-day time frame provided by 21 CFR 3.8.
† Includes two RFDs that were pending at the beginning of FY 2010. Does not include four requests for reconsideration for non-combination products that were issued within the 15-day time frame provided by 21 CFR 3.8.

Of the 32 combination product assignments issued, 23 combination products were determined to be drug-device combinations, 4 were determined to be drug-biologic combinations, 3 were determined to be device-biologic combinations, and 2 were determined to be drug-device-biologic combinations (see table below).

Determination	Drug-Device	Drug-Biologic	Device-Biologic	Drug-Device-Biologic	Total
Combination Products*****	23	4	3	2	**32**

* Includes four RFDs that were pending at the beginning of FY 2010. Does not include four requests for reconsideration for combination products that were issued within the 15-day time frame provided by 21 CFR 3.8.

Of the 12 non-combination product assignments issued, 7 were determined to be drugs, 3 were biologic/tissues, and 2 were devices (see table below).

Determination	Drug	Biologic	Device	Total
Non-Combination Products*	7	3	2	**12**

* Includes two RFDs that were pending at the beginning of FY 2010. Does not include four requests for reconsideration for non-combination products that were issued within the 15-day time frame provided by 21 CFR 3.8.

More detailed FY 2010 RFD performance information is available at the OCP Web site at http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm234257.htm.

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. The following information refers to FDA performance presented in this subsection.

- The number and types of combination products under review for FY 2010 by CBER, CDER, and CDRH included submissions filed or received in FY 2010. The number of combination product submissions is a small subset of the total number of submissions received by FDA.

- When reporting timeliness in days of the review for CBER-led or CDER-led combination products, PDUFA goals were referenced for priority and standard new drug applications (NDAs) and biologics license applications (BLAs). With CBER-led or CDRH-led combination products, MDUFA II Tier 2 decision goals were referenced for expedited and original premarket approval applications (PMAs) and premarket notifications [510(k)s].[4] To address priority and standard BLAs, MDUFMA I BLA decision goals for FY 2007 were referenced as no BLA-related goals were indicated in MDUFA II. Performance goals apply to only a subset of applications of a certain type. Therefore, not every application is required to be reviewed in accordance with a user fee-related time frame.

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

- Median review time was based on FDA first cycle review performance for PDUFA goals. For MDUFA II goals, median review times were based on total MDUFA II decision review time, except for BLAs where total decision review time was based on MDUFMA I goals. Actual review time was used when only one action was measured.

[4] Under MDUFA II, Tier 2 goals focus on completing the majority of reviews within longer time frames.

Timely and Effective Premarket Review

The table below reflects 311 original applications for NDAs, BLAs, PMAs, 510(k)s, investigational new drugs (INDs), investigational device exemptions (IDEs), and humanitarian device exemptions (HDEs) initially classified into one of nine categories of combination products received in FY 2010.[5]

Number and Types of Combination Products

Application Type	Combination Product Category									Totals
	1	2	3	4	5	6	7	8	9	
Original NDAs	4	12	--	1	--	--	--	--	--	**17**
Original BLAs	--	--	1	--	--	--	--	1	--	**2**
Original PMAs	2	--	--	3	2	--	2	--	1	**10**
Original 510(k)s	5	--	--	78	2	--	4	15	4	**108**
Original INDs	14	45	13	2	4	6	2	48	3	**137**
Original IDEs	--	--	--	21	1	--	6	8	1	**37**
Original HDEs	--	--	--	--	--	--	--	--	--	**0**
Totals	**25**	**57**	**14**	**105**	**9**	**6**	**14**	**72**	**9**	**311**

APPLICATION KEY:

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

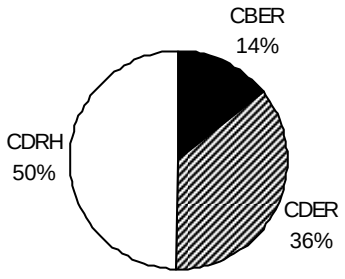
COMBINATION PRODUCT KEY:

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

Workload

Of the 311 original combination product applications, 44 applications were classified as CBER-led combination products; 112 applications were classified as CDER-led combination products; and 155 applications were classified as CDRH-led combination products.

Combination Product Applications



[5] The "Number and Types of Combination Products" received in FY 2009 are updated in Appendix A to reflect corrections and actions as of September 30, 2010.

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 MDUFA II established review performance goals for many types of drug, device, and biological product premarket applications. 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	Performance Level
PDUFA	NDAs	Priority	6 months	90%
		Standard	10 months	90%
	BLAs	Priority	6 months	90%
		Standard	10 months	90%
MDUFA II	Expedited PMAs	MDUFA II decision	280 days	90%
	PMAs	MDUFA II decision	295 days	90%
	510(k)s	SE or NSE decision	150 days	98%
	BLAs*	Priority	6 months	90%
		Standard	10 months	90%

* No specific performance goals for BLAs were provided under MDUFA II; therefore, the performance goal from FY 2007 under MDUFMA I was referenced.

FDA review performance information, with respect to premarket review, for CBER, CDER, and CDRH are based on a fiscal year receipt cohort. This methodology calculates performance information for submissions for the fiscal year FDA received them, regardless of when FDA acted on or approved the submissions. Review performance for submissions that are withdrawn or receive a refuse to file are not included in the statistics used to report performance. This section updates FDA's review performance on the FY 2009 combination product submissions and presents FDA's review performance on the FY 2010 combination product submissions through September 30, 2010.

Timely and Effective Premarket Review

Performance – CBER-led or CDER-led Combination Products

FY 2009 Submissions

FDA reviewed and acted on most (17 of 18) submissions identified as CBER-led or CDER-led combination products, and acted on most (15 of 17) of these submissions on time (see table below). These actions included 2 priority and 15 standard NDA combination product submissions. One standard NDA combination product submission was withdrawn.

Original Application Type	Review Type	Review Within (Months)	Number of Combination Products	Reviewed and Acted On	Number on Time	Median or Actual Review Time (Days)	Range of Review Time (Days)	
							Min	Max
NDAs	Priority	6	2	2	2	179	175	183
	Standard	10	16	15	13	302	278	530
BLAs	Priority	6	0	--	--	--	--	--
	Standard	10	0	--	--	--	--	--

FY 2010 Submissions

As of September 30, 2010, FDA reviewed and acted on almost half (8 of 17) of submissions identified as CBER-led or CDER-led combination products, and acted on all (8 of 8) of these submissions on time (see table below). These actions included four priority and four standard NDA combination product submissions. Two standard NDA combination product submissions received a refuse to file notification. Additional standard NDA and standard BLA combination product submissions were under review, with decisions pending.

Original Application Type	Review Type	Review Within (Months)	Number of Combination Products	Reviewed and Acted On	Number on Time	Median or Actual Review Time (Days)	Range of Review Time (Days)	
							Min	Max
NDAs	Priority	6	4	4	4	179	148	183
	Standard	10	11	4	4	302	258	303
BLAs	Priority	6	0	--	--	--	--	--
	Standard	10	2	0	--	--	--	--

Timely and Effective Premarket Review

Performance – CBER-led or CDRH-led Combination Products

FY 2009 Submissions

FDA reached decisions on virtually all (141 of 143) submissions identified as CBER-led or CDRH-led combination products, and reached decisions for most (136 of 141) of these submissions on time (see table below). These decisions included 1 original PMA combination product submission and 140 510(k) combination product submissions. One PMA and one 510(k) combination product submissions were under review, with a decision pending, as of September 30, 2010.

Original Application Type	Review Type	Review Within (Days)	Number of Combination Products	Decisions Reached	Number on Time	Median or Actual Review Time (Days)	Range of Review Time (Days)	
							Min	Max
Expedited PMAs	FDA decision	280	0	--	--	--	--	--
PMAs	FDA decision	295	2	1	1	52	52	52
510(k)s	SE or NSE	150	141	140	135	76	3	168

FY 2010 Submissions

As of September 30, 2010, FDA reached decisions on most (98 of 118) submissions identified as CBER-led or CDRH-led combination products, and reached decisions for most (97 of 98) of these submissions on time (see table below). These decisions included 98 510(k) combination product submissions. Additional PMA and 510(k) combination product submissions were under review, with decisions pending.

Original Application Type	Review Type	Review Within (Days)	Number of Combination Products	Decisions Reached	Number on Time	Median or Actual Review Time (Days)	Range of Review Time (Days)	
							Min	Max
Expedited PMAs	FDA decision	280	1	0	--	--	--	--
PMAs	FDA decision	295	9	0	--	--	--	--
510(k)s	SE or NSE	150	108	98	97	69	0	156

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 2010.[6]

Primary Assigned Center	Consulting Center			Number of Consults
	CBER	CDER	CDRH	
CBER	--	4	21	25
CDER	3	--	159	162
CDRH	3	276	--	279
Totals	6	280	180	466

As the primary assigned Center, CBER requested 25 intercenter consultations (4 consultations with CDER and 21 with CDRH); CDER requested 162 intercenter consultations (3 with CBER and 159 with CDRH); and CDRH requested 279 intercenter consultations (3 with CBER and 276 with CDER).

[6] 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 2010, 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. FDA received no formal requests to resolve a dispute regarding the timeliness of a combination product review during FY 2010. This year was the eighth straight year FDA received no formal requests. In addition to formal dispute requests, OCP may address disputes informally. Informal activities help prevent the need for formal dispute resolution.

APPENDIX A: Timely and Effective Premarket Review – Updated FY 2009 Data

The table below reflects 350 original applications for NDAs, BLAs, PMAs, 510(k)s, INDs, IDEs, and HDEs initially classified into one of nine categories of combination products received in FY 2009.

Number and Types of Combination Products

Application Type	Combination Product Category									Totals
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Original NDAs	4	12	--	1	--	--	1	1	--	**19**
Original BLAs	--	--	1	--	--	--	--	--	--	**1**
Original PMAs	--	--	--	1	--	--	1	--	--	**2**
Original 510(k)s	3	--	--	112	10	--	1	10	5	**141**
Original INDs	10	59	21	7	6	8	--	25	2	**138**
Original IDEs	1	--	1	19	5	--	10	11	1	**48**
Original HDEs	--	--	--	--	--	--	--	1	--	**1**
Totals	**18**	**71**	**23**	**140**	**21**	**8**	**13**	**48**	**8**	**350**

APPLICATION KEY:

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
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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

Of the 350 original combination product applications, CBER received and categorized as combination products 53 applications; CDER received and categorized as combination products 107 applications; and CDRH received and categorized 190 applications as of September 30, 2010.

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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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