FY 2007

Food and Drug Administration
Department of Health and Human Services

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 (FDA's) Fiscal Year (FY) 2007 Annual Report to Congress for the Office of Combination Products (OCP). This report includes the fourth 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. 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 that is 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 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 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.

Combination products will likely 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 reviewers in understanding this complex regulatory area.

FDA looks forward to ensuring 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, as required by 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 2007 highlighted in this report include the following:

- **Prompt Assignment of Combination Products.** In FY 2007, OCP continued to clarify the jurisdictional assignment of combination products. OCP published a jurisdictional update describing devices used to process human cells, tissues, and cellular and tissue-based products. OCP also published 11 Request for Designation (RFD) letters for approved or cleared products. Additionally, OCP continued to provide prompt RFD decisions. OCP issued 32 combination product RFD assignments with 100 percent of these assignments meeting the 60-day decision time requirement.

- **Timely and Effective Premarket Review.** In FY 2007, OCP continued to make significant contributions to the premarket review of combination products by directly facilitating complex review challenges. OCP also provided help and support to internal and external stakeholders by serving as an informal resource for combination product regulatory and process issues. Other OCP activities relating to premarket review include organizing a number of working groups to address specific regulatory issues pertaining to combination products. OCP chaired several working groups to delineate the regulatory pathway for injectors and for pharmacogenomic drug-diagnostic devices. OCP also participated in a number of FDA working groups examining issues related to data standards, nanotechnology, drug-eluting stents, artificial pancreas, premarket issues, product labeling, and wound care products.

- **Combination Product Review.** FDA received 333 original applications for combination products in FY 2007. This amount represents an increase of 42 percent from the 235 original applications for combination products in FY 2006. The number of intercenter consulting reviews increased to 390 for FY 2007 from 335 in FY 2006. This represents a 16 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. Accordingly, in FY 2007, OCP continued progress toward publication of the proposed rules. These proposed rules would clarify current good manufacturing processes and postmarket safety reporting requirements. OCP also chaired a working group considering postmarketing changes to combination products. Other activities undertaken by OCP include a variety of postmarketing and compliance related matters for 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. OCP also conducted activities that advance the development and review of innovative products associated with personalized medicine and FDA's Critical Path Initiative. Other activities include participation in FDA bioinformatics initiatives, participation in the development of a final rule on drug registration and listing, and planning a meeting with international regulatory agencies.

Throughout FY 2007, OCP strived 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 (FD&C 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 2007.

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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 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;

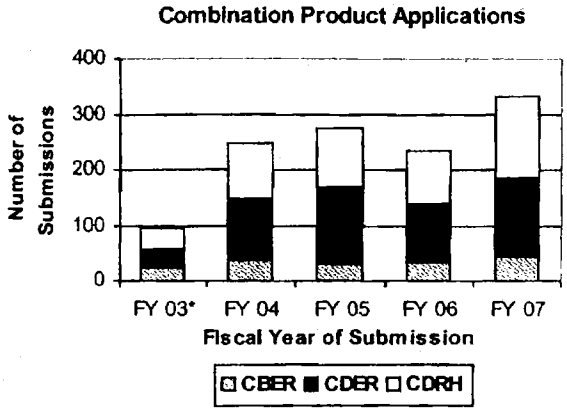
(2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

(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.

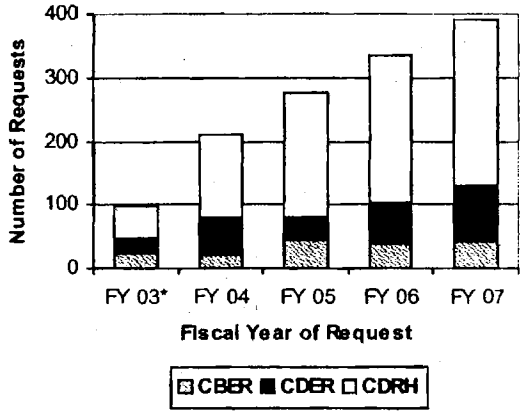
Combination products have the potential to provide enhanced therapeutic advantages compared to single entity devices, drugs, and biologics. More and more combination products are incorporating cutting-edge, novel technologies that hold great promise for advancing patient care. Combination products may include drug-delivery systems, gene therapy systems, personalized medicine drug, biological-device combinations, nanotechnology, and other innovative products for diagnostic and therapeutic treatments of cardiovascular, metabolic, oncologic, and other disorders. 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). Furthermore, some estimate 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 in FY 2007 increased, reaching a 5-year high (see corresponding graph). After decreasing by 14 percent from FY 2005 to FY 2006, the number of combination products submitted for review increased by 42 percent from FY 2006 (235) to FY 2007 (333). All three FDA Centers received increased applications for the review of combination products.



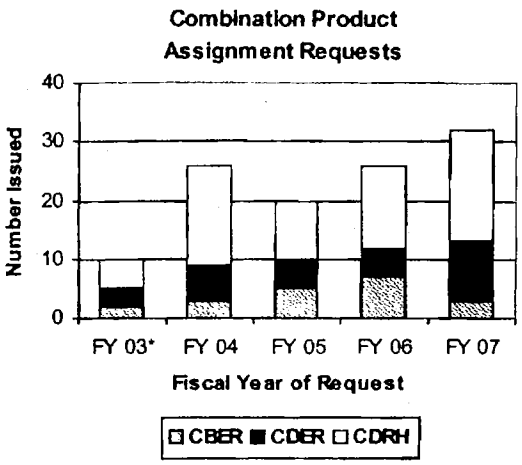
** Numbers do not represent all of FY 2003. FDA began data collection on April 1, 2003.*

More intercenter consults were included in combination product reviews. The number of intercenter consultation requests on combination products increased by 16 percent from FY 2006 (335) to FY 2007 (390), reaching a 5-year high (see graph below). 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 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. More details about intercenter consultation requests are presented in the following sections.



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

The number of combination product assignment requests issued in FY 2007 increased, reaching a 5-year high (see corresponding graph). The number of assignment requests issued increased by 23 percent from FY 2006 (26) to FY 2007 (32). Increases occurred for assignment requests issued to both the CDER and CDRH in FY 2007 while assignment requests issued to CBER decreased. More details about assignment requests are presented in the following sections.



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

Mandated Functions of OCP

FDA established OCP within the Office of the Commissioner's Office of International Activities and Strategic Initiatives 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 – 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

OCP experienced several significant staffing changes during FY 2007. Two key staff members resigned from government service and one new staff member joined OCP. The OCP Director departed in March 2007 and an Acting Director served for the remainder of the fiscal year (April 2007 through September 2007). The second departure was the Product Classification Officer in September 2007. A Scientific Reviewer joined OCP in March 2007. As of September 30, 2007, OCP was staffed by six permanent full-time positions. These positions include the Associate Director, a Product Assignment Officer, a Senior Advisor, two Scientific Reviewers, and a Program Support Specialist. Staffing plans include the immediate recruitment of a permanent Office Director. Also, FDA intends to provide for a projected total staffing size of 11 positions to meet the statutory responsibilities. 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.

Report on FY 2007 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 2007. Additionally, this section provides a performance assessment for combination product applications acted on in FY 2007. 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, 2007.

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 an internal database for documenting OCP's activities and e-mail records. The following summary illustrates the scope and breadth of OCP activities throughout the past fiscal year.

- **Documented approximately 600 OCP activities in FY 2007.**[1] These documented records include approximately 380 activities conducted with stakeholders external to FDA and 210 with internal stakeholders. As provided further in the report, the purpose of the contacts included jurisdictions/ assignments (approximately 150 contacts); premarket review issues (approximately 180 contacts); and postmarket regulation issues (approximately 70 contacts).

[1] These activities are in addition to a wide range of OCP activities associated with its review of and response to RFD.

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 2007 activities and impacts related to the assignment of combination products are as follows:

- **Issued all (100 percent) assignments, due as of September 30, 2007, within the 60 days provided by 21 CFR 3.8.** RFD performance data for the assignment of combination products in FY 2007 is found in the section of this report entitled, "Report on FY 2007 OCP Requirements, Prompt Assignment of Combination Products."

- **Published a jurisdictional update describing the assignment of devices used to process human cells, tissues, and cellular and tissue based products (HCT/Ps) at the point of care.** The jurisdictional update explains that devices intended to process HCT/Ps *ex-vivo* at the point of care to create a therapeutic article (that is, products where the intended therapeutic effect is mediated by the biologic output of the device) have been assigned to CBER. For example, cell sorters used at the point of care to isolate and/or concentrate autologous cells have been assigned to CBER for review under the device provisions of the FD&C Act. The jurisdictional update explained further that devices designed to isolate or concentrate a specific cell population have been assigned to CDRH for review under the device provisions of the FD&C Act when the sorted cells are intended for *in-vitro* diagnostic use. The jurisdictional update is available on the OCP Web site at: http://www.fda.gov/oc/combination/hct.html.

- **Reviewed comments submitted in response to a *Federal Register* (*FR*) 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 FD&C Act requires FDA to review each agreement, guidance,

[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).

or practice that is specific to the assignment of combination products to Centers and to determine whether the agreement, guidance, or practice is consistent with the requirements of the FD&C 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. On September 26, 2006, FDA published a *FR* notice requesting comments on its proposal to retain the CDER – CDRH and CBER – CDRH Intercenter Agreements as one of several sources of information as they continue to provide helpful nonbinding guidance. FDA proposed withdrawing the CBER – CDER Intercenter Agreement as the 2003 administrative transfer of many therapeutic biological products from CBER to CDER rendered that Intercenter Agreement out-of-date. OCP received and reviewed five comments in FY 2007. While all comments were favorable, two comments suggested that the CBER – CDER Intercenter Agreement not be withdrawn as it still provides helpful guidance, particularly with respect to the classification of certain types of products as drugs or biologics. As of September 30, 2007, OCP was considering the appropriate action to take in respect to the comments.

- **Published 11 additional RFD decision letters for products that have been approved or cleared.** FDA can only publish RFD decision letters for approved or cleared products. The RFD decision letters, posted on the OCP Internet site, are 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. Sixty-one letters are currently posted, and OCP plans to post additional letters on a regular basis. The letters are available on the OCP Web site at: www.fda.gov/oc/combination/rfd.html.

- **Continued to monitor and improve the internal processes to ensure the prompt and efficient review of RFDs.** OCP made minor modifications to the internal administrative document management process. These changes improve the document management process by enhancing efficiency.

- **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 approximately 150

stakeholder inquiries related to product jurisdiction/assignment, primarily by e-mail and telephone. The areas of inquiry encompassed the assignment process to resolving jurisdictional issues on a wide range of specific combination products. OCP received approximately the same number of inquiries about the jurisdictional process for combination products in FY 2007, as compared to FY 2006.

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 Web site at: www.fda.gov/oc/combination/consultative.html.

Premarket Review

OCP FY 2007 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 and provided guidance on the unique regulatory issues presented by combination products. OCP also facilitated and led or participated in meetings and discussions to ensure continued and consistent communication between sponsors and FDA review staff.

- **Responded to more than 180 contacts from Centers and sponsors relating to premarket review issues.** Approximately 64 percent of the contacts were from external stakeholders, and 36 percent of the contacts were from internal stakeholders. These activities included a number of specific issues that contribute to ensuring the timely and effective review of combination products. Examples include: clinical study design for drug-device evaluations, clinical trial monitoring approaches, co-packaged products, pre-filled 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. OCP facilitations addressed needs in areas such as the following: absorbable hemostatic agents, allergy, anesthesiology, antimicrobials (including antivirals), cardiology, dentistry, dermatology, drug delivery, gastroenterology, gene therapy, general surgery products, hematology/blood products, *in-vitro* diagnostics, iontophoresis, lock-flush products, metabolic disorders (for example, diabetes), nanotechnology, neurology, novel drug delivery systems, obstetrics and gynecology, oncology, orthopedics, ophthalmology, otolaryngology, pharmacogenomics, plastic surgery, photodynamic therapy, pulmonology, radiology, respiratory, urology, vaccine, and wound healing products.

- **Convened and chaired a working group to consider the scientific and regulatory issues for injectors.** Injectors are devices that are increasingly being developed to enhance the delivery of drugs or biological products. The working group is continuing its efforts by addressing the scientific and technical issues to establish the safety and effectiveness of such products and by clarifying the regulatory pathway for development of injectors and related drug and biological products. This work represents the next step prior to providing information for public stakeholder comments. Also in October 2006, FDA presented preliminary considerations on these issues at a Parenteral Drug Association Forum on the Universe of Prefilled Syringes and Injection Devices Forum (Bethesda, Maryland).

- **Continued 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," in cooperation with the Drug Information Association, OCP is continuing to develop clarifications on numerous public health and legal issues that were discussed at the meeting and in written comments submitted to OCP. In the interim, OCP frequently works with the Centers and the Office of Chief Counsel on a product-specific basis to develop approaches to resolve the difficult and complex legal and public health issues associated with determining when cross labeling is necessary when another sponsor's already approved product is involved. OCP is also continuing to develop information for stakeholder comment on the regulatory approaches for cross-labeling to ensure safety and effectiveness of differently regulated products.

- **Participated in numerous 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 2007 include: data standards, nanotechnology, drug eluting stents, artificial (computerized closed-loop)

pancreas, premarket issues, product labeling, and wound care products. Also, OCP participation in the antimicrobial working group contributed to an FDA guidance issued in July 2007 entitled, "Premarket Notification Submissions for Devices that Include Antimicrobial Agents."

- **Convened and chaired activities for pharmacogenomic drug-diagnostic device review and regulatory pathways.** Personalized medicine is a rapidly expanding therapeutic area and is one of the Department of Heath and Human Services (HHS) FY 2007 Departmental Objectives. Pharmacogenomics is a form of personalized medicine that utilizes specific testing technologies to guide and inform the use of certain drugs, biological products, and devices. OCP held a 2-day meeting in December 2006 with representatives of CBER, CDER, and CDRH to identify approaches to clarify and streamline the internal process for review of pharmacogenomic diagnostic tests. OCP also hosted recurring internal monthly intercenter pharmacogenomics meetings to address broad, cross-cutting issues for pharmacogenomic tests for use with drugs or biological products under active review in FDA.

- **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 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 by OCP 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 2007 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

390 intercenter consult requests in FY 2007, a 16 percent increase in workload over the prior fiscal year (see the section of this report entitled, "Report on FY 2007 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 under the Prescription Drug User Fee Act (PDUFA) and MDUFMA; identification and resolution of barriers to timely completion of consultation requests; and ensuring timely receipt of review documents by the consulting Centers.

- **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, diagnostic tests for personalized use of drug/biologic products, growth factors, injector delivery systems, metered-dose inhalers, pain management, medical imaging drugs and devices, metabolic-endocrine disorders, oncology, transcutaneous delivery systems, and wound care. Significant issues relating to the consult review process were facilitated in areas such as, coordination of premarket current good manufacturing practices (cGMP) inspections, certificates to foreign governments, eRoom, facilitation for groups that are new to the consult process, intercenter compliance consultations, and the regulatory approach for devices that enhance the safety of drug/biological products.

- **Formed working group to enhance internal procedures for the intercenter courier service.** The intercenter courier service is responsible for the delivery of review documents between different Centers that are more geographically dispersed. OCP formed the working group to enhance performance of the courier service for timely delivery of combination product regulatory documents to CBER, CDER, and CDRH in a manner that will better meet the needs of reviewers.

- **Conducted planning for a test of an automated system for tracking and managing intercenter consult requests.** The system is designed to enhance tracking of intercenter consults by providing a Web-based tracking system. A test of this system is scheduled for FY 2008.

Consistent and Appropriate Postmarket Regulation

MDUFMA requires OCP to ensure the consistency and appropriateness of postmarket regulation of combination products. OCP FY 2007 activities and impacts related to the consistency of postmarketing regulation are as follows:

- **Completed substantial work toward publication of proposed rule on cGMP for combination products.** The proposed rule would clarify and streamline cGMP requirements for combination products. The proposed rule is intended to 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 would generally meet the requirements of the device QS Regulation in 21 CFR 820. This will allow manufacturers the flexibility to select either the cGMP or QS 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 will 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.

- **Completed substantial work toward publication of proposed rule on postmarketing safety reporting requirements for combination products.** The proposed rule is intended to clarify the postmarket safety reporting requirements for combination products. The proposed rule will provide a framework for the reporting of adverse events for combination products and specify sponsors' reporting requirements for each type of combination product. Additionally, the proposed rule will 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 is intended to ensure the consistency and appropriateness of postmarket safety reporting for combination products while avoiding the need for duplicative reporting requirements.

- **Convened and chaired a working group to consider postmarketing changes to combination products.** During the postmarketing period, manufacturers often make a variety of changes to the approved/cleared combination product that may affect its safety and effectiveness. The internal working group is addressing the regulatory approach for post-approval modifications to an approved combination product and the type of submission to establish the safety and effectiveness

changes. This work represents the next step prior to providing information for public external stakeholder comments.

- **Undertook a variety of compliance-related and postmarketing activities to help ensure the safety and quality of combination products.** These include coordinating FDA responses to postmarket safety reports; providing guidance, facilitating, and leading meetings between industry and the Centers on cGMP requirements; responding to product defect issues; providing guidance on enforcement issues relating to the Prescription Drug Marketing Act and to import requirements; and providing warning letter guidance. For example, in one instance, OCP led an FDA ad hoc group to develop a postmarket safety response relating to fatal medication errors that resulted in the issuance of a Medication Safety Alert by the product manufacturer.

- **Provided clarification and support to Centers and sponsors to ensure consistent and appropriate postmarket regulation of combination products.** OCP responded to approximately 70 separate postmarket issues concerning the postmarket regulation of combination products. These issues included the application of cGMP and QS 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, labeling revisions, repackaging, off-label use and promotion, postmarket studies, and safety reporting.

Effective Resolution of Review Disputes

MDUFMA requires OCP to resolve disputes regarding the timeliness of the premarket review of a combination product. OCP FY 2007 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 staffs 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 2007.

Additional Activities and Impacts

Additional OCP activities and impacts in FY 2007 are as follows:

- **Advanced FDA's Critical Path to New Medical Products Initiative:**
    - *OCP continued to be active in interagency pharmacogenomics issues.* Apart from chairing an intercenter round table on pharmacogenomics,

OCP has assisted in defining the regulatory path for novel technology diagnostics and biomarkers under review for use with drug or biological products.

- *OCP continued to participate in the Interagency Task Force on Nanotechnology.* OCP staff attended the October 2006 public meeting on nanotechnology and contributed to the writing of a report on nanotechnology published in July 2007. FDA expects that many future nanotechnology products will be combination products. OCP is providing assistance in development of policy for these innovative products.
- *OCP represented FDA as a member of the Personalized Health Care Expert Panel Meeting held in March 2007.* The meeting was convened by HHS to provide assistance to the Office of Secretary on issues that may affect the implementation of personalized health care over the next 10 years.

- **Conducted 19 presentations to external stakeholders and 4 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; product development strategies; cGMP requirements; postmarket safety reporting requirements; and marketing application considerations, as well as discussion of OCP activities, initiatives, proposed regulations, and guidances. OCP presented at meetings organized by the:
  - American Association of Pharmaceutical Scientists
  - Association of Medical Device Manufacturers
  - Danish Embassy
  - Drug Information Association
  - Food and Drug Law Institute
  - Mayo Clinic
  - Mid-Atlantic Pharmaceutical and Biomedical Discussion Group
  - North Central Association of Food and Drug Officials
  - Parenteral Drug Association
  - Regulatory Affairs Professionals Society
  - Washington Pharma Liaisons Working Group
  - World Heath Organization/Pan American Health Organization

  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; impact of developing new technologies; cGMP for combination products; and adverse event

issues relating to combination products. OCP posts many of its presentations on the OCP Web site 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 in focused areas such as medical imaging, diabetes, diagnostic products, and novel technologies.
  - *Conducted periodic meetings with CBER, CDER, CDRH, and FDA senior executive management.* These meetings focused on key areas of combination products regulation and to discuss and help ensure support for OCP activities and initiatives.
- **Responded to several external and internal inquiries for reviews of journal articles, manuscripts, 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.
- **Actively participated in the advancement of FDA Bioinformatics Initiatives and in the development of the final rule on drug registration and listing.** OCP actively participated in three FDA-wide Commissioner-level business review boards with the goal of enhancing the electronic infrastructure necessary to facilitate the safety and effectiveness of combination products. Specifically, these activities are to promote the system design for postmarket adverse event safety reporting, consistency in the electronic regulatory submissions pertaining to combination products, and the infrastructure for ensuring product quality and appropriate registration and listing. OCP also actively participated in the FDA working group to oversee and develop a revised final rule on 21 CFR 207, establishment registration and product listing for human drugs.

- **Assisted in planning a Global Harmonization Task Force (GHTF) meeting scheduled for October 2007.** The need for effective global regulation of combination products is becoming more apparent. Industry is increasingly developing products that are intended to be marketed in several countries. Accordingly, differences in the regulatory path for combination products across regulatory bodies in different countries may act as a barrier to development of needed technologies and therapies. GHTF aims to harmonize the regulatory requirements across many different nations and alleviate some of the barriers to global product development. OCP assisted in planning the combination products session to be held at the October 2007 GHTF meeting (Washington, DC) to foster collaboration and understanding among the regulatory authorities of several nations.

Report on FY 2007 OCP Requirements

MDUFMA requires OCP to provide an annual performance assessment for combination product applications. This section provides performance information for FY 2007 and updates the FY 2006 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 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

Unless otherwise noted, all performance information in this section is as of September 30, 2007.

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

Four requests for assignment of a combination product were carried over from FY 2006 (pending and not overdue as of October 1, 2006). An additional 36 assignment requests for combination products were filed during FY 2007. Of the 40 potential assignment requests in FY 2007, 32 were issued with 3 to CBER, 10 to CDER, and 19 to CDRH (see table to the right). The remaining eight requests for combination products were pending and not overdue as of September 30, 2007.

Combination Product Assignment Requests	
Primary Center	**Number of Product Assignments**
CBER	3
CDER	10
CDRH	19
Pending	8
Total Requested	40

Prompt Assignment of Combination Products

Performance

All (32 of 32) product assignments were issued within the 60-day time frame, with a median assignment time of 32 days (see table below).[5] Of the 32 assignments issued, 26 combination products were determined to be drug-device combinations, 3 were device-biologic combinations, 1 was a drug-biologic combination, and 2 were drug-device-biologic combinations.

Combination Product Requests for Assignment						
Total Requests for Assignment Submitted*	Product Assignments Issued†	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)
40	32	8	0	100%	32	12 to 60

* Includes four RFDs that were pending at the beginning of the period.
† 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.
‡ Does not include one request for reconsideration received at the end of FY 2007 that was pending and not overdue as of September 30, 2007.

More detailed FY 2007 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] Assignment time is equal to the number of days from filing of the RFD to the issuance of the assignment letter.

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 2007 by CBER, CDER, and CDRH included applications FDA received in FY 2007. The number of combination product submissions is a small subset of the total number of submissions received by FDA.

- Only PDUFA goals for priority and standard new drug applications (NDAs) and biologics license applications (BLAs) are referenced in this report. For MDUFMA, only the decision goals for expedited and original premarket approval applications (PMAs), premarket notifications (510(k)s), and BLAs are referenced in this report. 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 PDUFA- or MDUFMA-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 (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).

- The MDUFMA decision goals for PMAs, including Expedited PMAs, are approval, approvable, approvable pending GMP inspection, not approvable, or denial. The MDUFMA decision goals for 510(k)s are substantially equivalent and not substantially equivalent.

- Median review time was based on FDA first cycle review performance for PDUFA goals. For MDUFMA goals, median review time was based on total MDUFMA decision review time. Actual review time was used when only one action was measured for both PDUFA and MDUFMA.

- All performance data in this report reflects FDA actions completed through September 30, 2007, unless otherwise specified.

Timely and Effective Premarket Review

The table below reflects 333 original applications for NDAs, BLAs, PMAs, 510(k)s, investigational new drugs (INDs), investigational device exemptions (IDEs), and humanitarian use exemptions (HDEs) initially classified into one of nine categories of combination products under review in FY 2007.[6]

Number and Types of Combination Products

Application Type	Combination Product Category									
	1	2	3	4	5	6	7	8	9	Totals
Original NDAs	4	8	--	--	--	--	--	2	--	**14**
Original BLAs	--	--	3	--	--	--	--	--	--	**3**
Original PMAs	--	--	--	4	--	--	--	--	--	**4**
Original 510(k)s	5	2	2	72	6	1	3	5	13	**109**
Original INDs	2	63	18	7	7	10	10	45	4	**166**
Original IDEs	2	--	1	12	10	--	7	2	2	**36**
Original HDEs	--	--	--	--	1	--	--	--	--	**1**
Totals	**13**	**73**	**24**	**95**	**24**	**11**	**20**	**54**	**19**	**333**

APPLICATION KEY:

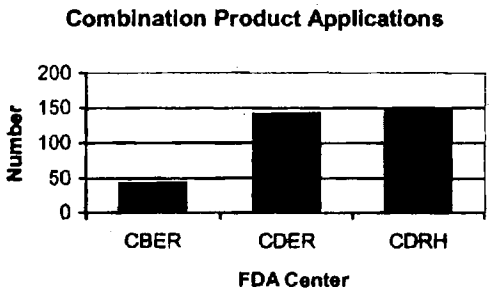
- **NDAs** = New Drug Applications
- **BLAs** = Biologics License Applications
- **PMAs** = Premarket Approval Applications
- **510(k)s** = Premarket Notifications
- **INDs** = Investigational New Drug Applications
- **IDEs** = Investigational Device Exemptions
- **HDEs** = Humanitarian Device Exemptions

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



[6] The "Number and Types of Combination Products" categorized for FY 2006 is updated in Appendix A.

Timely and Effective Premarket Review

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

FDA is required under MDUFMA 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. 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	
				FY 2006	FY 2007
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	MDUFMA decision	300 days	80%	90%
	PMAs	MDUFMA decision	320 days	80%	90%
	510(k)s	SE or NSE decision	90 days	75%	80%
	BLAs	Priority	6 months	75%	90%
		Standard	10 months	75%	90%

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 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 2006 combination product application submissions and presents FDA's review performance on the FY 2007 combination product application submissions through September 30, 2007.

Performance – CBER-led or CDER-led Combination Products

FY 2006 Submissions

FDA reviewed and acted on 14 of 15 submissions identified as CBER-led or CDER-led combination products (see table below). These actions included 1 priority and 12 standard NDA combination product submissions and 1 priority BLA combination product submission. One standard BLA combination product submission was under review, with a decision pending.

PDUFA Original Application Type	Review Type	Review Within	Reviewed and Acted On	Number on Time	Median or Actual Review Time (Days)	Range of Review Time (Days)	
						Min	Max
NDAs	Priority	6 months	1	1	179	179	179
	Standard	10 months	12	12	302	298	304
BLAs	Priority	6 months	1	1	183	183	183
	Standard	10 months	0	–	–	–	–

FY 2007 Submissions

As of September 30, 2007, FDA reviewed and acted on 5 of 17 submissions identified as CBER-led or CDER-led combination products (see table below). These actions included two priority and three standard NDA combination product submissions. Additional NDA and BLA combination product submissions were under review, with decisions pending. FDA will update the FY 2007 Submissions table in the FY 2008 OCP Performance Report.

PDUFA Original Application Type	Review Type	Review Within	Reviewed and Acted On	Number on Time	Median or Actual Review Time (Days)	Range of Review Time (Days)	
						Min	Max
NDAs	Priority	6 months	2	2	181	180	182
	Standard	10 months	3	3	303	265	304
BLAs	Priority	6 months	0	–	–	–	–
	Standard	10 months	0	–	–	–	–

Timely and Effective Premarket Review

Performance – CBER-led or CDRH-led Combination Products

FY 2006 Submissions

FDA reached decisions on 72 of 73 submissions identified as CBER-led or CDRH-led combination products (see table below). These decisions included 1 original PMA and 71 510(k)s combination product submissions. One PMA combination product submission was under review, with a decision pending.

MDUFMA Original Application Type	Review Type	Review Within	Decisions Reached	Number on Time	Median or Actual Review Time (Days)	Range of Review Time (Days)	
						Min	Max
Expedited PMAs	FDA decision	300 days	0	--	--	--	--
PMAs	FDA decision	320 days	1	1	192	192	192
510(k)s	SE or NSE decision	90 days	71	58	61	10	166
BLAs	Priority	6 months	0	--	--	--	--
	Standard	10 months	0	--	--	--	--

FY 2007 Submissions

As of September 30, 2007, FDA reached decisions on 61 of 110 submissions identified as CBER-led or CDRH-led combination products (see table below). All decisions made were on 510(k) combination product submissions, which have shorter review times. Additional PMA and 510(k) combination product submissions were under review, with decisions pending. FDA will update the FY 2007 Submissions table in the FY 2008 OCP Performance Report.

MDUFMA Original Application Type	Review Type	Review Within	Decisions Reached	Number on Time	Median or Actual Review Time (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	61	51	62	2	160
BLAs	Priority	6 months	0	--	--	--	--
	Standard	10 months	0	--	--	--	--

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 2007.[7]

		Consulting Center			Number of Consults
		CBER	CDER	CDRH	
Primary Assigned Center	CBER	–	9	33	42
	CDER	2	–	87	89
	CDRH	2	257	–	259
	Totals	4	266	120	390

As the primary assigned Center, CBER requested 42 intercenter consultations (9 consultations with CDER and 33 consultations with CDRH); CDER requested 89 intercenter consultations (2 with CBER and 87 with CDRH); and CDRH requested 259 intercenter consultations (2 with CBER and 257 with CDER).

[7] 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 2007, 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 2007. This was the fifth straight year no formal requests were received. The "Activities and Impacts for FY 2007, 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 2006 Data

The table below reflects 235 original applications for NDAs, BLAs, PMAs, 510(k)s, INDs, IDEs, and HDEs initially classified into one of nine categories of combination products under review in FY 2006.

Number and Types of Combination Products

Application Type	Combination Product Category									
	1	2	3	4	5	6	7	8	9	Totals
Original NDAs	1	12	--	--	--	--	--	--	--	13
Original BLAs	1	--	1	--	--	--	--	--	--	2
Original PMAs	--	--	--	2	--	--	--	--	--	2
Original 510(k)s	2	--	--	55	5	--	1	1	7	71
Original INDs	--	57	17	3	8	14	3	17	4	123
Original IDEs	1	--	--	8	10	--	3	--	1	23
Original HDEs	--	--	--	1	--	--	--	--	--	1
Totals	**5**	**69**	**18**	**69**	**23**	**14**	**7**	**18**	**12**	**235**

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
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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 235 original combination product applications, CBER received and categorized as combination products 35 applications; CDER received and categorized as combination products 104 applications; and CDRH categorized 96 applications, which were reviewed and acted on as of September 30, 2007.

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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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