FY 2005

PERFORMANCE REPORT TO CONGRESS

for the

Office of Combination Products

as required by the

Medical Device User Fee and Modernization Act of 2002

Commissioner's Report

I am pleased to submit the Food and Drug Administration's Fiscal Year (FY) 2005 Annual Report to Congress for the Office of Combination Products (OCP). This report includes the second full year of data since OCP was established as mandated by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA), enacted on October 26, 2002.

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

OCP continues to be actively involved in helping industry and FDA reviewers understand this complex regulatory area through a myriad of activities. OCP has made significant progress in enhancing the transparency and predictability of the process used to promptly assign combination products to a lead Center, facilitating interactions between industry and FDA to clearly delineate regulatory paths, and implementing processes to ensure the timely and effective review, and consistent and appropriate postmarket regulation of combination products.

In addition, OCP continues to engage stakeholders through various mechanisms, by seeking comments and providing clarification on a number of difficult issues surrounding the regulation of combination products. OCP co-sponsored a public workshop held in May 2005 to discuss the issue of mutually conforming labeling for combination products consisting of components developed and marketed by different manufacturers. OCP solicited stakeholder comment on options for determining the appropriate number of marketing applications for combination products and options for addressing the differences in drug, device, and biological product postmarket safety reporting regulations. Also, OCP published a guidance document providing mechanisms to reduce application user fees for certain innovative combination products, and a guidance document to explain the type of information sponsors should submit in a Request for Designation so OCP can make timely and appropriate product assignment decisions.

OCP closely monitored the timeliness of the consultation processes between Centers, offering advice and support to industry and agency review staff on challenging combination product issues. OCP's efforts this year garnered the following comment in *Medical Devices and Diagnostic Industry* magazine, May 2005: "OCP is open-minded and flexible about many complex issues regarding the regulation of combination products. So, stakeholders should seek contact with OCP staff as a valuable and often-informal resource for information and guidance." We look forward to continued success in meeting the unique challenges in the review and regulation of combination products.

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

Executive Summary

The Food and Drug Administration (FDA) established the Office of Combination Products (OCP) on December 24, 2002, in response to the Medical Device User Fee and Modernization Act of 2002 (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 2005 highlighted in this report include the following:

- **Prompt Assignment of Combination Products**. OCP implemented a number of new processes to enhance the transparency and predictability of the assignment process. FDA published a final rule defining "primary mode of action" (PMOA), the statutory criterion FDA must use when assigning a combination product to a Center for review and regulatory oversight. OCP also published a guidance document for stakeholders on the Request for Designation (RFD) process, which incorporates the PMOA concepts and explains the type of information needed to assign a product to the appropriate Center. One hundred percent of the OCP assignments issued in FY 2005 met the 60-day decision time requirement.

- **Timely and Effective Premarket Review**. OCP published a final guidance document providing information on user fees for combination product applications. The guidance provides mechanisms to reduce the application fee burden for certain innovative combination products. OCP also published final guidance to provide sponsors with information on submitting and resolving formal disputes regarding the timeliness of the premarket review of combination products. In addition, on its Internet site, OCP solicited stakeholder comments on possible options for determining when it is appropriate to submit a single marketing application or separate marketing applications for the various components of a particular combination product. OCP conducted a public workshop to obtain input from stakeholders and other experts on mutually conforming labeling, a complex regulatory issue for combination products. OCP continued to provide support to sponsors and Centers on a variety of products presenting complex regulatory issues to facilitate the timely and effective premarket review of combination products. Additionally, OCP continued to actively monitor the consultation process for combination products under review, facilitated the timely completion and provision of constructive feedback on intercenter requests for consult reviews, and facilitated the development of processes outlining consult review responsibilities and issues to be addressed for specific product areas. Centers initially categorized

275 original applications as combination products in FY 2005. All (80 of 80) of the combination product marketing applications reviewed and acted on in FY 2005 were within the review targets. Recent examples of approved combination products can be found at http://www.fda.gov/oc/combination/approvals.html.

- **Consistent and Appropriate Postmarket Regulation**. On its Internet site, OCP solicited stakeholder comments on possible options to address the differences in drug, device, and biological product postmarket safety reporting regulations. Comments submitted in response to a draft guidance document on current good manufacturing practices for combination products were considered, along with options for further implementation of this initiative. OCP established a working group to consider how to address stakeholder inquiries regarding the advertising and promotion of combination products. OCP supported sponsors and Centers by clarifying manufacturing and adverse event reporting regulations and other postmarketing issues related to specific products.

OCP continued to conduct internal and external outreach activities through a variety of educational and informational presentations for both FDA staff and stakeholders. Throughout this fiscal year, OCP endeavored to ensure the prompt assignment of combination products to Centers, the timely and effective premarket review of such products, and the consistent and appropriate postmarket regulation of these products. These activities help provide patient access to innovative technologies and address unmet medical needs through the timely delivery of safe and effective combination products to the public.

Table of Contents

Introduction 1

Overview of Combination Products 3

Mandated Functions of the Office of Combination Products (OCP) 4

OCP Organizational Structure 5

Report on FY 2005 OCP Activities and Impacts 7

Activities and Impacts for FY 2005 8

Prompt Assignment of Combination Products 8

Timely and Effective Premarket Review 11

Premarket Review 11

Consultative/Collaborative Review Process 14

Consistent and Appropriate Postmarket Regulation 14

Effective Resolution of Review Disputes 16

Additional Activities and Impacts 16

Report on FY 2005 OCP Requirements 19

Prompt Assignment of Combination Products 20

Timely and Effective Premarket Review 22

Effective Resolution of Review Disputes 27

Appendices

Appendix A: Timely and Effective Premarket Review – Updated FY 2004 Data

Appendix B: Glossary

Appendix C: Summary of Footnotes

Introduction

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

MDUFMA also requires FDA to submit an annual report to Congress on the activities and impact of OCP. This document fulfills this requirement for FY 2005.

(This page left blank intentionally.)

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 defined in 21 CFR 3.2(e):

(1) Products comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

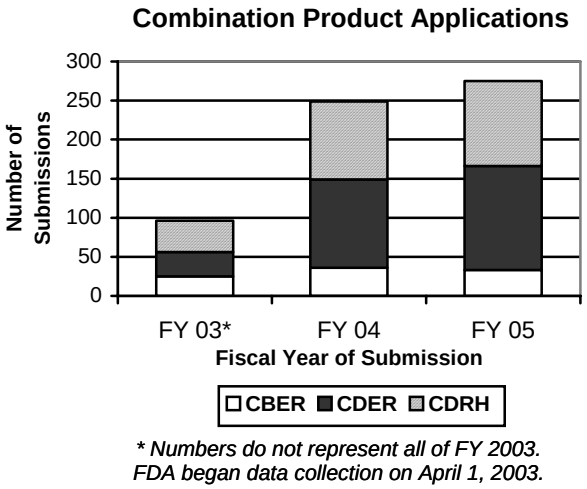
(2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

(3) A drug, device, or biological product packaged separately that, according to its investigational plan or proposed labeling, is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose;

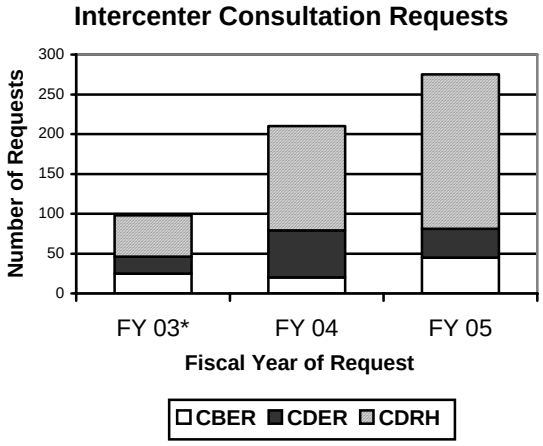
(4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

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

FDA is receiving significantly more combination products for review. In the last year alone, the number of combination products under review increased by 10 percent (249 to 275, see graph to the right), and the number of intercenter consultation requests on combination products has increased by 31 percent (210 to 275, see graph below). Since combination products involve components (biologics, drugs, and devices) that would normally be regulated under different types of regulatory authorities, and frequently by different FDA Centers[1], 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.



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



Mandated Functions of the Office of Combination Products

FDA established OCP within the Office of the Commissioner's Office of International Activities and Strategic Initiatives (OIASI) on December 24, 2002. MDUFMA established broad responsibilities for OCP that cover the regulatory life cycle of drug-device, drug-biologic, and device-biologic combination products, and include product jurisdiction decisions and specific premarket review and postmarket processes. However, the primary responsibilities for scientific review and regulation of combination products remain in one of three product Centers – the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiological Health (CDRH) – to which they are assigned by OCP.

[1] When Center or Centers is used, it refers to the FDA Center or FDA Centers.

Specifically, the statute (503(g)(4)(B-F)) requires OCP to:

1. Promptly assign a Center with primary jurisdiction for a combination product.

2. Ensure the timely and effective premarket review of combination products, by overseeing the timeliness of and coordinating reviews involving more than one Center.

3. Ensure the consistency and appropriateness of postmarket regulation of combination products.

4. Resolve disputes regarding the timeliness of premarket review of combination products.

5. Review and update agreements, guidance documents or practices specific to the assignment of combination products.

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

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

OCP Organizational Structure

As of September 30, 2005, OCP, within OIASI, is staffed by seven permanent full-time positions. In addition to a Director of OCP, these positions include an Associate Director/Medical Officer, a Product Assignment Officer, a Product Classification Officer, a Senior Scientific Advisor, a Program Analyst, and a Program Support Specialist. (OCP staff members are identified on the OCP Internet under Frequently Asked Questions: http://www.fda.gov/oc/combination/faqs.html#_Toc88444658). Work plans provide for an eventual projected staffing size of ten positions when financial resources to support such needed expansion are available. The office is located at: 15800 Crabbs Branch Way, Suite 200, HFG-3, Rockville, MD 20855, (301) 427-1934, fax (301) 427-1935, email: combination@fda.gov.

(This page left blank intentionally.)

Report on FY 2005 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 2005. Additionally, this section provides a performance assessment for combination product applications acted on in FY 2005. 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, 2005.

Activities and Impacts for FY 2005

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 PMOA.[2] By submitting a 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.[3] 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 2005 activities and impacts related to the assignment of combination products are as follows:

- **All (100 percent) assignments, due as of September 30, 2005, were issued within the 60 days provided by 21 CFR 3.8.** RFD performance data for the assignment of combination products in FY 2005 is found in the section of this report entitled "Report on FY 2005 OCP Requirements, Prompt Assignment of Combination Products."
- **Published a final rule describing how FDA assigns a lead Center with responsibility for premarket review and regulation of a combination product.** The Final Rule was published in the *Federal Register* on August 25, 2005, and became effective November 23, 2005 (http://www.fda.gov/OHRMS/DOCKETS/98fr/05-16527.htm). The Final Rule amends the combination product regulations to define "mode of action" (MOA) and PMOA. It fulfills the statutory requirement to assign products based on their PMOA, and uses safety and effectiveness issues, as well as consistency with the regulation of similar products, to guide the assignment of products when FDA cannot determine with reasonable certainty which mode of action provides the most important therapeutic action of the combination product. The Final Rule is intended to promote the public health by codifying FDA's criteria for the assignment of combination products in transparent, consistent, and predictable terms.

[2] This is in accordance with section 503(g)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(g)(1).

[3] The RFD process is outlined in 21 CFR Part 3. Information required in an RFD submission is outlined in 21 CFR 3.7.

- **Published a guidance document entitled "Guidance for Industry and FDA Staff: How to Write a Request for Designation (RFD)."** This guidance was posted on the OCP Internet site on August 31, 2005 (http://www.fda.gov/oc/combination/howtowrite.html). The goal of this guidance is to help a sponsor understand the type of information FDA needs to determine the regulatory identity of a product as a drug, device, biological product, or combination product, and to assign the product to the appropriate Center for review and regulation. This guidance should serve to reduce the number of incomplete RFDs by clarifying the type of information OCP needs to makes its decision. The guidance incorporates the requirements of the final rule defining the PMOA of a combination product (PMOA Final Rule) published in the *Federal Register* on August 25, 2005.

- **Published a jurisdictional update to explain the current context of the Intercenter Agreements (ICAs)**. At the time they were written in 1991, the ICAs explained how various categories of both combination and single-entity medical products were classified (as a biologic, a drug, a device or a combination product) and assigned to a lead Center for premarket review and regulation. OCP has considered and is implementing a variety of mechanisms to provide greater transparency in jurisdictional decision making. One of the options considered was to update to ICAs. However, as explained in this jurisdictional update published on the OCP Internet site (http://www.fda.gov/oc/combination/intercenterupdate.html), OCP believes that the goal of robust transparency will likely be better served by means other than updating the ICAs. The process of updating the ICAs would be time consuming, and given the quick pace of product development, the revisions would again soon be out of date. For these reasons, OCP believes that transparency would likely be better served by clearly articulating the principles upon which jurisdictional determinations are based, and by providing specific examples of jurisdictional determinations that help illustrate these principles. Examples include capsular descriptions of jurisdictional decisions, redacted FDA decision letters for RFDs, detailed statements of the classification and assignment of product classes, and others as provided in the additional OCP activities as described in this section. While the ICAs should not be independently relied upon as the most current, accurate jurisdictional statements, they are still helpful in certain situations, and continue to be available at www.fda.gov/oc/combination/intercenter.html. As required by Section 503(g)(4)(F) of MDUFMA, FDA will consult with stakeholders and determine whether to continue in effect, modify, review, or eliminate the ICAs, and publish in the *Federal Register* a notice with its final determination. OCP plans to conduct this stakeholder consultation process in early 2006.

- **Published 128 additional capsular descriptions of selected jurisdictional decisions.** These descriptions of selected RFD decisions serve to update the examples provided in the ICAs and are intended to improve the transparency of the jurisdiction process. In selecting which jurisdictional determinations were appropriate to summarize and make public, OCP considered the extent to which the product could be suitably described, the extent to which the existence and description of the product or similarly described products has been made public, and other related factors. The descriptions are grouped by Center and cover both combination and non-combination products. OCP will

continue to update the list of capsular descriptions as new decisions are made and as information on these products becomes publicly available. The current list contains 198 capsular descriptions, and is available at http://www.fda.gov/oc/combination/determinations.html.

- **Published 42 RFD decision letters for products that have been approved or cleared.** The RFD decision letters, posted on the OCP Internet site, were redacted to remove trade secret and confidential commercial information in accordance with the Freedom of Information Act. 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. The letters are available at http://www.fda.gov/oc/combination/rfd.html.

- **Convened and chaired an intercenter working group to consider the definition of "chemical action," a key determinant of whether a product is a device or a drug**. One of the distinctions between the statutory drug and device definitions is that a device cannot achieve its primary intended purposes through chemical action within or on the body of man, or be dependent on being metabolized to achieve its primary intended purposes. The goal of this working group is to further clarify what is meant by "chemical action within or on the body" contained in the statutory definition of a device. Such clarification should be helpful to sponsors in determining whether a product meets the definition of a drug or a device.

- **Published a jurisdictional update concerning Metered Dose Inhalers, Spacers, and Other Accessories.** This document, published on the OCP Internet site at http://www.fda.gov/oc/combination/mdiupdate.html, provides clarification on the regulation of metered dose inhalers (MDIs) and accessories to be used with MDIs, such as spacers, actuators, spacers incorporating actuators, dose counters, and locking clips.

- **Continued to streamline the internal process and timeline for the prompt and efficient review of RFDs.** Developed and instituted the use of a new RFD checklist, based on the final PMOA rule, for use upon the receipt of an RFD. This process ensures an expeditious filing review and response to sponsors.

- **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, RFD's and other jurisdictional decisions pending or made in the Centers, and enhances the consistency and clarity of jurisdictional decisions across FDA.

- **Responded to external and internal stakeholder inquiries by providing advice, guidance, and clarification on a variety of informal requests related to the assignment of combination products.** OCP responded to over 195 stakeholder inquiries on issues ranging from the assignment process itself to jurisdictional issues on a wide range of specific combination products in areas including orthopedic, neurology, pulmonology, allergy, anesthesiology, cardiology, dermatology, dentistry, endocrinology, obstetrics and gynecology, urology, radiology and imaging, photodynamic therapy, in vitro diagnostics, tissue engineering, gene therapy, vaccine, orphan products, iontophoresis, antimicrobials (including antivirals), wound healing products, pain management products, hemostatic agents, and novel drug delivery systems. This represents an increase of 11 percent in the number of inquiries in FY 2005, as compared to FY 2004, related to the assignment of combination products.

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 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 at http://www.fda.gov/oc/combination/consultative.html.

Premarket Review

OCP FY 2005 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**. Fostered early interactions between industry and FDA to develop clearly delineated regulatory schemes for the development and expeditious review of marketing submissions for combination products. Responding to requests from both industry and FDA review staff, OCP consulted on the unique regulatory issues presented by combination products and facilitated meetings and discussions to ensure continued and consistent communication between sponsors and review staff.

- **Facilitated communication between Centers and sponsors**. OCP facilitated meetings and communications on a number of specific issues and products that contribute to ensuring the timely and effective review of combination products. Examples included: handling of changes to product design, product specifications, test methods, or indications for use; chemistry, manufacturing and controls (CMC); preclinical protocol reviews; new delivery systems for approved drugs; clarification of labeling requirements; review standards; over-the-counter drugs; user fees; pharmacogenomics; nanotechnology;

novel drug delivery technology; tissue engineering; pre-filled syringes, cross-labeling, drug eluting stents, orphan products, software, and Master Files. The combination products addressed needs in the following areas: pediatrics, urology, orthopedics, oncology, pulmonology, anesthesiology, ophthalmology, cardiology, endocrinology, neurology, in vitro diagnostics, antimicrobial therapy, gynecology, radiology and imaging, tissue products, vaccines, drug delivery, and wound-healing products.

- **Published a final guidance document entitled "Guidance for Industry and FDA Staff: Application User Fees for Combination Products."** The final guidance document was announced in the *Federal Register* on April 21, 2005. The guidance incorporates stakeholder comments received in response to the draft guidance published in September 2004, and provides information on marketing application user fees for combination products. In particular, the document describes how the Prescription Drug User Fee Act (PDUFA) "barrier to innovation" waiver provision may be applied in the infrequent situation where two marketing applications are necessary for an innovative combination product. This waiver provides a reduction in application user fees equivalent to the additional fee burden associated with the submission of two applications. The guidance document is available at http://www.fda.gov/oc/combination/userfees.html.

- **Conducted a public workshop in cooperation with the Drug Information Association (DIA) entitled "Combination Products and Mutually Conforming Labeling."** This workshop, held May 10, 2005, brought together experts from FDA and throughout regulated industry to obtain stakeholder input on this complex regulatory issue. An increasing number of combined uses for drugs and devices, drugs and biological products, or devices and biological products are being developed where the two products are independently approved, manufactured, and distributed. In some cases, when one product is already approved for a particular indication, route of administration or dose, another sponsor may develop a separate product to be used with the approved product for an indication, route of administration or dose different from the one specified in the current labeling of the approved product. Workshop sessions provided an interactive forum to discuss both the public health and legal issues that arise when considering whether or not mutually conforming labeling is necessary for independently marketed products intended to be used together. The public health issues addressed a number of factors related to ensuring the safe and effective use of both products together, including consistent labeling, adequate instructions for use, and monitoring reformulation or redesign, while the legal issues focused on factors such as cooperation between manufacturers, use of proprietary information, product misbranding, and exclusivity. Comments from both the workshop and the public docket are being reviewed and analyzed, and FDA is currently considering appropriate next steps.

- **Solicited stakeholder comment on the number of marketing applications for a combination product.** On the OCP Internet site, OCP solicited stakeholder input as FDA considers the development of policies on this subject. Depending upon the type of combination product, approval, clearance, or licensure can be obtained through submission of a single marketing application, or through separate marketing applications for the individual constituent parts of the combination product. For most combination products, a single marketing application will usually be sufficient for the combination product's approval, clearance, or licensure. In some cases, however, a sponsor may choose to submit two marketing applications when one would suffice, while in other cases FDA may determine that two marketing applications are necessary. FDA is considering numerous factors as it develops policy in this area. FDA's discussion and solicitation of comments are available at http://www.fda.gov/oc/combination/singlesepconpaper.html.
- **Published a Frequently Asked Questions (FAQs) section on the OCP Internet site.** OCP developed questions and answers to address a variety of issues related to the review, regulation, and assignment of combination products, as well as other frequently received inquiries from the public, stakeholders, and FDA review staff. This section, consisting of over 30 FAQs, was posted on November 7, 2004, updated, and is available at http://www.fda.gov/oc/combination/faqs.html.
- **Participated in various intercenter working groups clarifying issues related to combination products.** The working groups are developing policies and guidances for the development, jurisdiction and assignment, and/or regulatory review of a variety of new technologies and classes of combination products. Topics covered by specific working groups include nanotechnology, pharmacogenomics, antimicrobial coatings, and wound care products.
- **Served as a resource for FDA staff on the appropriate use and interpretation of the combination product categorization algorithm and associated categories.** The categories for combination products are based on the types of regulatory issues the products present, for example, a prefilled drug or biologic delivery system, a device physically combined with a drug or biologic, a co-packaged product or kit, or separate products with mutually conforming labeling. All premarket applications in CBER, CDER, and CDRH are categorized as to whether or not they concern a combination product, and if so, what type.
- **Analyzed monthly reports from CBER, CDER, and CDRH capturing data on the categorization of combination products.** Data on new product applications in CBER and CDER and completed product applications in CDRH are reviewed to ensure that combination product categories are being accurately assigned. Discrepancies are reported to the Centers for correction to ensure the accuracy of the data reported annually to Congress on the numbers and types of combination products under review, as required by MDUFMA. OCP instituted a new process of receiving corrected reports monthly to facilitate data collection for the annual report to Congress. 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 2005 activities and impacts related to the consultative/collaborative review process are as follows:

- **Provided support to review staff to facilitate the intercenter consultation process.** Examples include clarifying internal operating procedures, roles and responsibilities, updating the intercenter consult request form to ensure appropriate distribution of both requests and completed consults, ensuring continued effective performance of the courier service for delivery of consult requests to CDER personnel at FDA's new White Oak facility, identification of consulting divisions and contacts, clarification of due dates and completion status, facilitating access to electronic review documents, clarification of specific review requirements, and identification and resolution of barriers to timely completion of consultation requests.
- **Facilitated intercenter communication and procedures to delineate the consult review process and issues to be considered for specific product areas.** These include wound care solutions and wound dressings, bone growth factors for orthopedic and dental indications, steroid eluting leads, and diagnostic breath tests. Provided training and coordination to establish the working processes and procedures for an eRoom to facilitate the sharing and real-time review of applications, and an eRoom to facilitate the sharing of Master Files between reviewers in different Centers consulting on combination product reviews. These mechanisms provide for enhanced communication across Centers utilizing different databases and tracking systems that cannot readily be linked.
- **Actively monitored the intercenter consultation process on combination products under review to ensure that the requesting Center received timely and constructive feedback**. OCP tracked and followed up on a total of 275 intercenter consult requests in FY 2005, a 31 percent increase in workload over the prior fiscal year (see the section of this report entitled "Report on FY 2005 OCP Requirements, Timely and Effective Premarket Review" for the consult requests by Center).

Consistent and Appropriate Postmarket Regulation

MDUFMA requires OCP to ensure the consistency and appropriateness of postmarket regulation of combination products. OCP FY 2005 activities and impacts related to the consistency of postmarketing regulation are as follows:

- **Solicited stakeholder comment on Postmarket Safety Reporting for Combination Products**. On the OCP Internet site, OCP solicited stakeholder input as FDA considers the development of policies on this subject. To ensure consistent and appropriate postmarket regulation and appropriate ongoing assessment of risks, FDA is considering mechanisms by which the postmarket safety reporting requirements ordinarily associated with the marketing application used to approve or clear a combination product may be supplemented, as appropriate, to take into account the combination nature of the product. The differences in the drug, device, and biological product postmarket safety reporting regulations that FDA is considering for

supplementation currently are Device Malfunction Reporting, 5-Day MDR Reporting, Drug and Biological Product "Alert" Reporting, and reporting of Blood Related Deaths. FDA is seeking input on this assessment and other options for adverse event reporting for combination products. FDA's discussion and solicitation of comments are available at http://www.fda.gov/oc/combination/adveventconcept.html.

- **Participated in an FDA working group developing recommendations for changes to the MedWatch forms 3500 and 3500A for reporting adverse events.** Recommended changes to the forms that will help to identify adverse events associated with combination products in order to facilitate appropriate intercenter communication, review, and analysis of adverse events. A new form (3500A MedWatch) for use by user facilities, importers, distributors, and manufacturers for mandatory reporting was effective October 2005, and will, for the first time, collect data that identifies products as combination products.
- **Reviewed docket comments submitted in response to the publication of the draft guidance document "Guidance for Industry and FDA: Current Good Manufacturing Practice for Combination Products."** Compiled and analyzed stakeholder comments concerning the draft recommendations for achieving compliance with applicable good manufacturing practice requirements for a combination product. Conducted meetings with the cross-Center working group that collaborated with OCP in the development of the draft guidance document to discuss the comments and consider options to move forward with this initiative.
- **Established an intercenter working group to consider the advertising and promotion of combination products**. The regulatory framework for prescription drug labeling and advertising varies from the regulatory framework for the labeling and advertising of medical devices. Sponsors have asked FDA to explain their regulatory responsibilities for the advertising and promotion of combination products consisting of both a drug and a device. This working group was established to consider the differences between existing drug and device regulations governing advertising and promotion and how these would apply to a combination product. In addition, the group is considering internal mechanisms for communicating information across Centers concerning the advertising and promotion of combination products or their constituent components.
- **Provided clarification and support to Centers and sponsors to ensure consistent and appropriate postmarket regulation of combination products.** Specific areas include the application of current good manufacturing practices (cGMP) and quality systems (QS) regulations for compliance inspections of combination products, appropriate mechanisms and manufacturer responsibilities for reporting adverse events, requirements for registration and listing, post-approval changes, labeling revisions, repackaging, inspection requirements, and off-label use and promotion of combination products.

Effective Resolution of Review Disputes

MDUFMA requires OCP to resolve disputes regarding the timeliness of the premarket review of a combination product. OCP FY 2005 activities and impacts related to the effective resolution of review disputes are as follows:

- **Published a final guidance document entitled "Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product."** This document, announced in the *Federal Register* on April 11, 2005, describes a premarket timeliness dispute as arising when FDA does not review and act on an applicant's submission within the applicable performance goal set by PDUFA or MDUFMA. The guidance incorporates the comments received from stakeholders in response to the draft guidance published in September 2004. The document includes the timelines and process for presenting a dispute resolution to OCP, information that should be included in a timeliness dispute resolution request, and how OCP will follow up and respond to such requests. This document is available at http://www.fda.gov/oc/combination/dispute.html.
- **Facilitated the resolution of issues presented informally by sponsors concerning the timeliness of premarket review of combination products.** Facilitated communications between sponsors and FDA review staff to identify, clarify, and resolve specific concerns associated with review timeliness. These activities helped prevent the need for more formal dispute resolution.

Additional Activities and Impacts

Additional OCP activities and impacts in FY 2005 are as follows:

- **Advanced FDA's Critical Path to New Medical Products Initiative:**
  - Served on the Steering Committee for program development of the FDA/Drug Information Agency (DIA) Pharmacogenomics in Drug Development and Regulatory Decision Making – Workshop 3, conducted on April 11-13, 2005. Served as a member of the FDA Interdisciplinary Pharmacogenomic Review Group. Participated in the development of a concept paper on drug/diagnostic co-development, and served as a moderator for the workshop track discussing issues related to the draft concept paper.
  - Served as a member of the interagency working group on nanotechnology. FDA expects that many nanotechnology products will be combination products. Participated in the development of the FDA and Nanotechnology Products FAQs. Responses to over 20 FAQs are published on the FDA Internet site at http://www.fda.gov/nanotechnology/faqs.html.
- **Served on an interagency working group to develop a Scientific Reviewer page for the new FDA Portal.** Participated in working group meetings and provided input on the development of a scientific reviewer webpage that would incorporate all existing resources and tools to help FDA review staff to do their jobs more efficiently.

- **Conducted 27 presentations to external stakeholders and 10 presentations to FDA staff for education, outreach, and training purposes.** Stakeholder presentations focused on the assignment and regulation of combination products and discussion of OCP activities, initiatives, proposed regulations, and guidances. Internal presentations were focused on raising awareness of combination product issues, including the intercenter consultation process; the identification and categorization of combination product applications; and jurisdiction issues and GMP considerations for combination products. This represents a 23 percent increase in the number of outreach activities compared to a total of 30 in FY 2004. Recent OCP presentations are posted at http://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, biologic, 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, dispute resolution, and future industry needs.
  - Conducted periodic meetings with CBER, CDER, CDRH, and FDA senior executive management to discuss key areas of combination products regulation and to discuss and ensure support for OCP activities and initiatives.
  - Met with other FDA senior executive management officials to brief them on OCP roles, responsibilities, and ongoing initiatives.

- **Authored two articles explaining the current status of the regulation of combination products.** "Combination Products: Challenges and Progress" (http://www.fda.gov/oc/combination/aug05_09_combinations.html), an article published in the *Regulatory Affairs Focus Magazine* and an editorial entitled, "FDA's Office of Combination Products: Roles, Progress & Challenge" (http://www.fda.gov/oc/combination/jmdr2005.html), published in the *Journal of Medical Device Regulation*, were intended to provide stakeholders with an update of current progress and future OCP activities to clarify the regulation of combination products.

- **Responded to a variety of external inquiries and internal requests for reviews of journal articles and other 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 a number of requests for interviews concerning combination product regulation and OCP roles and responsibilities.** Responded to press inquiries from a variety of trade press, technology, and scientific journals and publications seeking information about various aspects of how combination products are regulated.

(This page left blank intentionally.)

Report on FY 2005 OCP Requirements

MDUFMA requires OCP to provide an annual performance assessment for combination product applications. This section provides performance statistics for FY 2005. Unless otherwise noted, all performance data in this section are as of September 30, 2005. 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

The following information refers to all FDA performance presented in this section.

- OCP, CBER, CDER, and CDRH developed a process to collect the necessary data and report on the required information enacted in MDUFMA. This process was implemented April 1, 2003.
    - CBER's and CDER's data collection systems identify combination product status when applications are submitted for review. Review performance statistics are based on a fiscal year receipt cohort; this methodology calculates performance statistics for applications for the fiscal year FDA received them, regardless of when FDA ultimately acted on or approved the submissions.
    - CDRH's data collection system records this information at application close-out (when review decisions are made). Review performance statistics are based on the fiscal year when decisions are made or the close-out of the applications; this methodology calculates performance statistics for applications for the fiscal year FDA made decisions on them, regardless of when FDA received the applications.

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 a 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

There were 6 requests for assignment of products carried over from FY 2004 (pending and not overdue as of October 1, 2004), and 15 requests received during FY 2005 for a total of 21 requests. All but 1 (20 of 21) assignment were issued in FY 2005, with 5 combination products assigned to CBER, 5 to CDER, and 10 to CDRH (see table to the right). One request was pending and not overdue as of September 30, 2005.

Combination Product Assignment Requests	
Primary Center	**Number of Product Assignments**
CBER	5
CDER	5
CDRH	10
Pending	1
Total Requested	**21**

Of the 20 assignments issued, 13 combination products were determined to be drug-device combinations and 7 were device-biologic combinations.

Prompt Assignment of Combination Products

Performance

All (20 of 20) product assignments issued were within the 60-day time frame, with a median assignment time of 44 days (see table below). Assignment time is equal to the number of days from receipt of the RFD to the issuance of the assignment letter.

Combination Product Requests for Assignment						
Total Requests for Assignment Submitted[4]	Product Assignments[5] 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)
21	20	1	0	100%	44	11 to 59

More detailed FY 2005 RFD performance information, including OCP's review of RFDs for non-combination products, is available at http://www.fda.gov/oc/combination/fy05rfd.html.

[4] Includes six that were pending at the beginning of the period.
[5] Does not include one request for reconsideration that was issued within the 15-day time frame provided by 21 CFR 3.8.

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 table below reflects the number of original applications for NDAs, BLAs, PMAs, 510(k)s, INDs, IDEs, and HDEs initially classified into one of nine categories of combination products in FY 2005.[6] FDA initially categorized 275 original applications under review as combination products.

Number and Types of Combination Products

Application Type	Combination Product Category									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**TOTALS**
Original NDAs	1	8	--	1	--	1	1	--	--	**12**
Original BLAs	1	--	1	--	--	--	--	--	--	**2**
Original PMAs	--	--	--	2	--	--	--	--	--	**2**
Original 510(k)s	5	--	--	55	9	--	6	--	3	**78**
Original INDs	1	42	14	7	4	12	17	54	1	**152**
Original IDEs	1	--	--	19	7	--	1	1	--	**29**
Original HDEs	--	--	--	--	--	--	--	--	--	**0**
TOTALS	**9**	**50**	**15**	**84**	**20**	**13**	**25**	**55**	**4**	**275**

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:

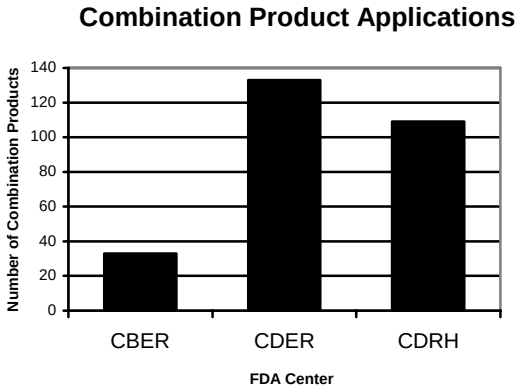
- **1 = convenience kit or co-package**
- **2 = prefilled drug delivery device/system**
- **3 = prefilled biologic delivery device/system**
- **4 = device coated/impregnated/otherwise combined with drug**
- **5 = device coated or otherwise combined with biologic**
- **6 = drug/biologic combination**
- **7 = separate products requiring mutually conforming labeling**
- **8 = possible combination based on mutually conforming labeling of separate products**
- **9 = other type of combination product**

[6] The "Number and Types of Combination Products" categorized for FY 2004 is updated in Appendix A.

Timely and Effective Premarket Review

Workload

Of the 275 original combination product applications, CBER received and categorized 33 applications as combination products; CDER received and categorized 133 applications as combination products; and CDRH categorized 109 applications as combination products, which were reviewed and acted on as of September 30, 2005.



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 target for original NDAs, BLAs, PMAs, and 510(k)s.

Application Type	Review Type	Review Within
Original NDAs	Priority	6 months
	Standard	10 months
Original BLAs	Priority	6 months
	Standard	10 months
Original PMAs	Expedited	180 days
	Original	180 days
Original 510(k)s	N/A	90 days

The FDA review performance statistics for the fiscal year cohorts are calculated differently for the Centers:

- CBER and CDER – review performance statistics are based on a fiscal year receipt cohort; this methodology calculates performance statistics for applications for the fiscal year FDA *received* them, regardless of when FDA ultimately acted on or approved the submissions. Therefore, the timeliness in days of the review for combination products are reported using the PDUFA review performance goals.[7]
- CDRH – review performance statistics are based on the fiscal year when marketing authorization decisions are made; this methodology calculates performance statistics for applications for the fiscal year FDA *made final determinations* on them, regardless of when FDA received the applications. Since MDUFMA performance goals relate to when submissions are received, for purposes of this report, the timeliness in days of the review for combination products is reported using the statutory review performance targets.[7]

Because both approaches report on a specific fiscal year cohort, the statistics shown for a particular year may change from one report to the next.

[7] For an update on FY 2005 review performance for the Prescription Drug User Fee Act (PDUFA) and the Medical Device User Fee and Modernization Act of FY 2002 (MDUFMA), please see the PDUFA FY 2005 Report to Congress and the MDUFMA FY 2005 Report to Congress at http://www.fda.gov.

Timely and Effective Premarket Review

Performance - CBER and CDER Combination Products

As of September 30, 2005, all combination product submissions filed in FY 2005 were still pending and not overdue (see table below). It is too early to report review performance for FY 2005.[8]

Application Type	Review Type	Review Within	Reviewed and Acted On	Number on Time	Number Pending and Not Overdue	Median Review Time (days)	Range of Review Time[9] (days)
Original NDAs	Priority	6 months	--	--	2	--	--
	Standard	10 months	--	--	10	--	--
Original BLAs	Priority	6 months	--	--	1	--	--
	Standard	10 months	--	--	1	--	--
Original 510(k)s	N/A	90 days	--	--	--	--	--

Performance - CDRH Combination Products

The table below reflects FDA's performance for original PMAs and 510(k)s for combination product submissions reviewed and acted on in FY 2005.[10]

- FDA reviewed and acted on all (2 of 2) PMAs for combination products within the 180-day statutory review performance target.
- FDA reviewed and acted on all (78 of 78) 510(k)s for combination products within the 90-day statutory review performance target.

Application Type	Review Type	Review Within	Reviewed and Acted On	Number on Time	Median Cycle Review Time[11] (days)	Range of Review Time (days)
Original PMAs	Expedited	180 days	--	--	--	--
	Original	180 days	2	2	128	72 to 178

[8] The "Performance - CBER and CDER Combination Products" table for submissions received in FY 2004 is updated in Appendix A.

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

[10] Considers whether FDA review time remained within 180 days for Original and Expedited PMAs and 90 days for 510(k)s, with FDA's review clock being reset whenever additional information is received in accordance with 21 CFR 814.37 for PMAs and 21 CFR 807.87(1) for 510(k)s.

[11] Median cycle review time is based on all FDA review cycles.

Original 510(k)s	N/A	90 days	78	78	43	3 to 90

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 2005. As the primary assigned Center, CBER requested 45 Intercenter Consultations (9 consultations with CDER, 36 consultations with CDRH); CDER requested 36 Intercenter Consultations with CDRH; and CDRH requested 194 intercenter consultations (9 with CBER, 185 with CDER).

		Consulting Center			Number of Consults
		CBER	CDER	CDRH	
Primary Assigned Center	CBER	--	9	36	45
	CDER	--	--	36	36
	CDRH	9	185	--	194
	Totals	9	194	72	275

The monitored Intercenter Requests for Consultative or Collaborative Review forms represent a 31 percent increase over FY 2004 (210 consults), and are indicative of the number of premarket reviews of combination products that involved a consulting Center.[12]

[12] 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 2005, 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 2005. While this was the third straight year no formal requests were received, the "Activities and Impacts for FY 2005, 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.

(This page left blank intentionally.)

APPENDIX A: Timely and Effective Premarket Review – Updated FY 2004 Data

In FY 2004, FDA categorized 248 original applications under review as combination products. The table below reflects the number of original applications classified into one of nine combination product categories for original NDAs, BLAs, PMAs, 510(k)s, INDs, IDEs, and HDEs.

Number and Types of Combination Products

Application Type	Combination Product Category									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**TOTALS**
Original NDAs	2	12	--	2	--	--	1	--	--	**17**
Original BLAs	1	--	--	--	--	--	--	--	--	**1**
Original PMAs	--	--	--	3	1	--	1	1	--	**6**
510(k)s	1	1	--	50	4	--	6	2	5	**69**
Original INDs	2	43	11	5	11	6	12	25	11	**126**
Original IDEs	---	1	--	16	7	--	1	2	--	**27**
Original HDEs	--	--	--	--	2	--	--	--	--	**2**
TOTALS	**6**	**57**	**11**	**76**	**25**	**6**	**21**	**30**	**16**	**248**

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**

Of the 248 original combination product applications, CBER received and categorized as combination products 36 applications; CDER received and categorized as combination products 112 applications; and CDRH categorized 100 applications, which were reviewed and acted on as of September 30, 2004.

APPENDIX A: Timely and Effective Premarket Review – Updated FY 2004 Data

Performance - CBER and CDER Combination Products

The table below reflects FDA's performance for original NDAs, BLAs, and 510(k)s for combination product submissions that were received in FY 2004 and reviewed and acted on through September 30, 2005.

- FDA reviewed and acted on all (2 of 2) priority NDAs for combination products within the 6-month review target.
- FDA reviewed and acted on all (15 of 15) standard NDA and one (1 of 1) standard BLA for combination products within the 10-month review target.
- FDA reviewed and acted on 1 of 2 original 510(k)s for combination products within the 90-day review target.

Application Type	Review Type	Review Within	Reviewed and Acted On	Number on Time	Number Pending and Not Overdue	Median or Actual Review Time (days)	Range of Review Time[8] (days)
Original NDAs	Priority	6 months	2	2	--	180	177 to 182
	Standard	10 months	15	15	--	303	106 to 396
Original BLAs	Priority	6 months	--	--	--	--	--
	Standard	10 months	1	1	--	301	--
Original 510(k)s	N/A	90 days	2	1	--	93	80 to 105

APPENDIX B: Glossary

Biologics License Application (BLA) – An application submitted when an applicant wishes to obtain marketing approval for a biological product.

Humanitarian Device Exemption (HDE) – An application that is similar to a premarket application (PMA), but exempt from the effectiveness requirements of a PMA. An approved HDE authorizes marketing of a Humanitarian Use Device (HUD).

Investigational Device Exemption (IDE) – An IDE allows an investigational device to be used in a clinical study.

Investigational New Drug (IND) – An application that a drug sponsor must submit to FDA before beginning tests of a new drug on humans. The IND contains the plan for the study and is supposed to give a complete picture of the drug, including its structural formula, animal tests results, and manufacturing information. It serves as a request for an exemption from the federal statute that prohibits an unapproved drug or biological product from being shipped in interstate commerce.

New Drug Application (NDA) – The application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the United States. The data gathered during the animal studies and human clinical trials of an IND become part of the NDA.

Premarket Approval Application (PMA) – An application containing sufficient valid scientific evidence to ensure that a class III medical device is safe and effective for its intended use.

Premarket Notification [510(k)] – A submission to demonstrate that a device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device that is not subject to premarket approval. Applicants must compare their 510(k) device to one or more similar devices currently on the U.S. market and make and support their substantial equivalency claims.

APPENDIX C: Summary of Footnotes

[1] When Center or Centers is used, it refers to the FDA Center or FDA Centers.

[2] This is in accordance with section 503(g)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(g)(1).

[3] The RFD process is outlined in 21 CFR Part 3. Information required in an RFD submission is outlined in 21 CFR 3.7.

[4] Includes six that were pending at the beginning of the period.

[5] Does not include one request for reconsideration that was issued within the 15-day time frame provided by 21 CFR 3.8.

[6] The "Number and Types of Combination Products" categorized for FY 2004 is updated in Appendix A.

[7] For an update on FY 2005 review performance for the Prescription Drug User Fee Act (PDUFA) and the Medical Device User Fee and Modernization Act of FY 2002 (MDUFMA), please see the PDUFA FY 2005 Report to Congress and the MDUFMA FY 2005 Report to Congress at http://www.fda.gov.

[8] The "Performance - CBER and CDER Combination Products" table for submissions received in FY 2004 is updated in Appendix A.

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

[10] Considers whether FDA review time remained within 180 days for Original and Expedited PMAs and 90 days for 510(k)s, with FDA's review clock being reset whenever additional information is received in accordance with 21 CFR 814.37 for PMAs and 21 CFR 807.87(1) for 510(k)s.

[11] Median cycle review time is based on all FDA review cycles.

[12] 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 2005, as reported in the previous section.

Department of Health and Human Services
Food and Drug Administration

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

Office of Planning (HFP-10)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
Phone: 301-827-5270
FAX: 301-827-5260

This report is available on the FDA Home Page at http://www.fda.gov
and OCP's Home Page at http://www.fda.gov/oc/combination