OFFICE OF COMBINATION PRODUCTS

ANNUAL REPORT TO CONGRESS

Federal Food, Drug, and Cosmetic Act

as amended by the

Medical Device User Fee and Modernization Act of 2002

October 26, 2003

Food and Drug Administration
Department of Health and Human Services

Executive Summary

On October 26, 2002, Congress enacted the Medical Device User Fee and Modernization Act (MDUFMA). MDUFMA required the FDA to establish an office to ensure the prompt assignment of combination products (drug-device, biologic-device, drug-biologic, or drug-device-biologic products) to agency Centers, the timely and effective premarket review of such products, and consistent and appropriate postmarket regulation of these products. MDUFMA also requires FDA to submit an annual report to Congress on the activities and impact of this office. This document is submitted to Congress in fulfillment of this requirement for the first such report due not later than one year after the date of enactment of the legislation.

In response to MDUFMA, FDA established the Office of Combination Products (OCP) within the Office of the Commissioner on December 24, 2002. OCP activities and impacts through July 31, 2003, highlighted in this report include the following:

- **Prompt Assignment of Combination Products**. OCP implemented a variety of measures to optimize the assignment process, and is developing for public review and comment a definition of "primary mode of action," the statutory criterion FDA must use when assigning a combination product. OCP received 12 requests for assignment of products determined to be combination products. All (100%) of the 10 Center assignments issued met the 60-day decision time requirement (one request was withdrawn and one was still within the 60-day period and pending assignment as of July 31, 2003). Mean and median total FDA assignment times were 36.9 days and 39 days, respectively.

- **Timely and Effective Premarket Review**. OCP provided support to sponsors and agency Centers on a variety of products presenting complex regulatory issues to facilitate the premarket review process for these products. The Office actively monitors the consultation process on combination products under review to ensure that the requesting center receives timely and constructive feedback. In addition, OCP has drafted tips for agency reviewers for successful intercenter consultations. OCP formed internal agency working groups to develop policy and guidance related to premarket review issues. OCP also worked with agency Centers to modify their information systems to collect certain information required by MDUFMA, such as the numbers, types and timeliness of reviews for combination products.

- **Consistent and Appropriate Postmarket Regulation**. OCP formed internal agency working groups to develop policy and guidance related to postmarket issues. One of these working groups established a process to ensure appropriate communication and consultation between Center postmarket reviewers. Information contained in OCP assignment decision letters was expanded to provide sponsors with a better understanding of the scope of regulatory requirements for their combination product.

In addition, OCP has implemented several educational and outreach efforts targeting stakeholders and FDA staff. Through all of their activities this year, OCP has striven to ensure the prompt assignment of combination products to agency Centers, the timely and effective premarket review of such products, and the consistent and appropriate postmarket regulation of these products to ensure the

timely delivery of safe and effective combination products to the American public. These and other activities are described in more detail in the report that follows.

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Introduction

On October 26, 2002, Congress enacted the Medical Device User Fee and Modernization Act (MDUFMA). In amending the Federal Food, Drug, and Cosmetic Act, MDUFMA provided FDA with new responsibilities, resources, and challenges. Among other things, MDUFMA required the 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, the 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 requires FDA to submit an annual report to Congress on the activities and impact of OCP. The agency is submitting this document in fulfillment of the requirement for the first such report. This report is due not later than one year after the date of enactment of the legislation. In the future, FDA will prepare this report following the end of each fiscal year to meet the annual reporting requirement.

Overview of Combination Products

Combination products are increasingly incorporating cutting edge, novel technologies that hold great promise for advancing patient care. These products are defined by any of the following criteria:[1]

(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.

For example, innovative drug delivery devices have the potential to make treatments safer or more effective, or more convenient or acceptable to patients. Drug-eluting cardiovascular stents have the potential to reduce the need for surgery by preventing the restenosis that often occurs following stent implantation. Drugs and biologics can be used in combination potentially to enhance the safety and/or effectiveness of either product used alone. Biologics are being incorporated into novel orthopedic implants to help facilitate the regeneration of bone required to permanently stabilize the implants.

Stakeholder Concerns: Combination Product Regulation

Stakeholders report that FDA can expect to receive significantly more combination products for review as technological advances continue to merge therapeutic product areas and blur the historical lines of review responsibility for products regulated by specific FDA Centers. Because combination products involve components that would normally be regulated under different regulatory authorities and frequently by different FDA Centers, they also raise challenging regulatory, policy, and review management issues. A number of criticisms have been raised regarding FDA's regulation of combination products. These include concerns about the consistency, predictability, and transparency of the process used to assign an FDA Center with primary responsibility for review and regulation of a combination product; issues related to the management of the review process when two (or more) FDA Centers have review responsibilities for a combination product; lack of clarity about the postmarket

regulatory controls applicable to combination products; and lack of clarity regarding certain agency policies, such as when applications to more than one Center are needed.

Establishing the Office of Combination Products (OCP)

On October 26, 2002, Congress enacted the Medical Device User Fee and Modernization Act (MDUFMA). To address stakeholder concerns regarding the review and regulation of combination products, section 204 of MDUFMA required the 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. FDA established OCP within the Office of the Commissioner's Office of International Activities and Strategic Initiatives on December 24, 2002. The legislation establishes broad responsibilities for OCP that cover the entire regulatory life cycle of drug-device, drug-biologic, device-biologic, and drug-device-biologic combination products, and include oversight of product jurisdiction decisions and specific premarket review and postmarket processes. However, the primary responsibilities for review and regulatory oversight of a specific combination product 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 it is assigned.

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

1. Promptly assign an agency 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 by coordinating reviews involving more than one agency 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 assumed and continues the functions of the Combination Products Program previously established within the FDA's Office of the Ombudsman. These functions include working with the Centers to develop guidance and/or regulations to clarify the agency's lead Center assignment and regulation of combination products.

In addition, the Office of the Commissioner consolidated the product jurisdiction program within OCP in June 2003. OCP is now responsible for agency action on all Requests for Designation (RFD) submitted by industry in accordance with 21 CFR Part 3. This includes requests for classification of a product as a biological product, device or drug, as well as requests for lead Center assignment of combination products.

[1] As defined in 21 CFR § 3.2(e).

OCP Organizational Structure

OCP is currently staffed by six permanent positions. In addition to a Director, these positions include an Associate Director/Medical Officer, a Product Assignment Officer, a Product Classification Officer, a Program Analyst, and a Secretary. An additional scientific position is currently vacant. Work plans provide for an eventual projected staffing size of ten positions. The new office is located at: 15800 Crabbs Branch Way, Suite 200, HFG-3, Rockville, Maryland 20855, (301) 827-9229, fax (301) 827-9230, email: combination@fda.gov.

Report on FY 2003 OCP Activities and Impacts

This document reports the activities and impacts of OCP in the assignment of combination products and in coordinating the review and regulation of combination products reviewed by CBER, CDER and CDRH since the establishment of OCP on December 24, 2002. This document also provides a preliminary performance assessment on combination product applications submitted after April 1, 2003, the implementation date for the identification of combination products in the agency's premarket databases[2]. 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 Post-Market Regulation
- Effective Resolution of Review Disputes

Unless otherwise noted, all performance data in this section are as of July 31, 2003, the cut-off date for data collection for this report.

[2] CDER and CBER began identifying combination products upon receipt as of April 1, 2003. CDRH began identifying combination products at close-out as of May 1, 2003.

Prompt Assignment of Combination Products

MDUFMA requires OCP to promptly assign a Center with primary jurisdiction for a combination product and to review and update agreements, guidance documents, or practices specific to the assignment of combination products. In accordance with section 503(g)(1) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 353(g)(l)), the agency is required to assign premarket review responsibility for combination products based on the product's "primary mode of action." Existing intercenter agreements provide guidance on some combination product assignments. By submitting a "Request for Designation" (RFD), a company may obtain a formal agency determination of a combination product's primary mode of action and of assignment of the lead Center for the product's premarket review and regulatory oversight. FDA (through OCP) will make its jurisdictional determination within 60 days of filing the RFD.[3] Companies and FDA Centers may also informally request assistance from OCP in working out difficult jurisdictional issues not raised in an RFD submission.

Performance

Since the establishment of OCP on December 24, 2002, twelve requests for assignment of products determined to be combination products have been received[4]. Ten of the products were determined to be drug-device combinations, one is a device-biologic combination, and one is a drug-biologic combination. Of these twelve requests, ten assignments have been issued (two to CBER, three to CDER, and five to CDRH). Of the two remaining requests, one was withdrawn from consideration and the other was still pending (not overdue) as of July 31, 2003. Total FDA combination product assignment time is equal to the number of calendar days from receipt of an RFD submission by a sponsor to the date of issuance of the letter in which OCP designates a lead Center assignment. All (100%) of the assignments due as of July 31, 2003, were issued within the 60-days provided in 21 CFR § 3.8. Time spent assigning combination products to Centers ranged from 29 to 46 days. The average assignment time for these 10 combination products was 36.9 days. Median assignment time for these products was 39 days.

[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] Data is through July 31, 2003.

Assignment of Combination Products December 24, 2002, through July 31, 2003				
Total Requests for Assignment Submitted*	**Assignments Issued****	**Assignments Pending (not overdue)**	**Assignments Pending (overdue)**	**Issued on Time (%)**
12	10	1	0	**100%**
* Total does not include one request for reconsideration that was responded to within 15-day timeframe provided in 21 CFR § 3.8 **One application was withdrawn.				

Additional Activities and Impacts

Since the establishment of OCP in December 2002, several steps have been taken to initiate, track, and improve combination product assignment. OCP's FY 2003 activities and impacts related to the assignment of combination products are as follows:

- **Published a final rule to reflect the transfer of responsibility for the product jurisdiction program from the Office of the Ombudsman to OCP in the June 23, 2003 *Federal Register*, revising 21 CFR Part 3**. The new regulation also provides an address for electronic submission of RFD's concurrent with their formal submission to OCP.
- **Formed and chairs an internal agency working group to develop a definition for "primary mode of action."** Primary mode of action is the statutory criterion to be used in assigning an agency component (e.g., Center) to have lead premarket review responsibility for a combination product. However, the term is not defined in statute or regulation. This working group is comprised of members from OCP, CBER, CDER, CDRH, and the Office of Chief Counsel (OCC) and is tasked with developing clearer standards for FDA to apply in making jurisdictional decisions. It is expected that this process will result in proposed rulemaking to revise 21 CFR Part 3 to include a definition of "primary mode of action." FDA's goal is to improve the consistency, predictability, and transparency of the process used to assign combination products to FDA Centers.
- **Established an internal process and timeline for the prompt and efficient review of RFDs for the assignment of the lead agency Center for combination products**. Revised the screening and filing process for receipt of an RFD and established an internal review process and deadlines for OCP, OCC, and Center reviews and responses, to help ensure jurisdictional determinations are made within 60 calendar days of receipt.

- **Expanded the information provided in assignment decision letters to provide sponsors with a better understanding of the scope of regulatory requirements for their products**. OCP letters have been expanded to provide the agency's preliminary determination of GMP and adverse event reporting requirements, when such determinations can be made at the time of assignment.
- **Began developing an internal database of RFD determinations to facilitate the timely consideration of new assignment requests**.
- **Resumed a routine monthly product jurisdiction meeting for the exchange of information between OCP jurisdictional and assignment specialists and the product jurisdiction officers in CBER, CDER, and CDRH**. This venue provides for an open discussion of, and progress report on, pending Requests for Designation and other related jurisdictional decisions pending or made in the Centers to enhance the consistency and clarity of jurisdictional decisions across the agency.
- **Responded to a variety of external and internal stakeholder inquiries related to the assignment of combination products**. These requests varied from queries on the assignment process itself to jurisdictional issues on a wide range of combination products including, for example, implants with drug and biologic components, cancer therapies, and novel drug delivery modalities.

Timely and Effective Premarket Review

MDUFMA requires OCP to ensure the timely and effective premarket review of combination products by overseeing the timeliness of and coordinating reviews involving more than one agency Center. On July 31, 2002, FDA issued a standard operating procedure outlining 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. The document defines key terms such as consultation and collaboration and describes key policies regarding the consultative/collaborative review process, as well as responsibilities and procedures to be followed by those requesting and conducting intercenter reviews. The first revision of this document, effective February 14, 2003, implemented interim measures to provide for the tracking of consultative and collaborative reviews of combination products by OCP. The document will continue to be refined and updated. This document is available at http://www.fda.gov/oc/combination/consultative.html.

Performance

When MDUFMA was enacted, the agency's existing pre-market submission databases did not capture all of the types of information required by MDUFMA. In response, OCP, CBER, CDER and CDRH developed a process to collect the necessary data and report on the required information. This process was implemented beginning April 1, 2003. CBER's and CDER's data collection systems identify applications as containing a combination product at the time of application submission. CDRH's data collection system records this information at application close-out (when review decisions are made).

Prevalence of Combination Products

From April 1, 2003, to July 31, 2003, the agency received for review 49 original applications preliminarily categorized by the Centers as combination products[5]. Of these, CBER received 23 applications, CDER received 15 applications, and CDRH made final decisions on 11 applications. Each combination product is classified into one of nine categories (see category key in chart below) using a categorization methodology developed for this purpose.

	Combination Product Category									
Application Type[6]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**TOTALS**
Original NDA		2								**2**
Original BLA			2							**2**
Original PMA										**0**
510(k)				1			2		1	**4**
Original IND	2	6	5		3	4	4	4	4	**32**
Original IDE	1		1	1	3	0	2		1	**9**
Original HDE										**0**
TOTALS	**3**	**8**	**8**	**2**	**6**	**4**	**8**	**4**	**6**	**49**

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

[5] Data figures are based on application receipt cohort. Figures for PMAs, 510(k)s, IDEs, and HDEs are subject to change due to CDRH's practice of tracking/reporting at application close-out.
[6] NDA = New Drug Application, BLA = Biologics License Application, PMA = Premarket Approval Application, 510(k) = Premarket Notification, IND = Investigational New Drug Application, IDE = Investigational Device Exemption, HDE = Humanitarian Device Exemption

Product Review: Preliminary Performance

It is too early to report meaningful review performance statistics for most marketing applications submitted since implementation of agency tracking systems for combination products (April 1, 2003). Insufficient time for review has passed for final decisions to be made on any original NDA, BLA, or PMA combination product applications received since this date.

Preliminary review performance data is available for 510(k) applications. Final decisions have been made by CDRH on four combination product 510(k) applications since May 1, 2003. All (100%) of these applications were reviewed within their established timeframes.

			COMBINATION PRODUCTS			
APPLICATION TYPE			**Applications Received (#)**[7]	**Application Reviews Completed (#)**	**Review Time (Days)**	**Reviewed On Time (%)**
Original NDAs	Priority		0	---	---	---
	Standard		2	0	---	---
Original BLAs	Priority		0	---	---	---
	Standard		2	0	---	---
Original PMAs	Expedited		0	---	---	---
	Regular		0	---	---	---
510(k)s	Traditional	90 days	3	3	34, 39, 90	100%
	Special	30 days	1	1	45 (total)	100%[8]
	Abbreviated	90 days	0	0	---	---
TOTALS			**8**	**4**		**100%**

[7] The cut-off date for data collection was July 31, 2003. The number of original PMA and 510(k) applications received during this period may change due to CDRH's practice of tracking/reporting at application close-out.

[8] Considers whether FDA review time remained within 30 days for a Special 510(k)s (90 days for Traditional and Abbreviated 510(k)s), with FDA's review clock being reset to zero whenever additional information is received in accordance with 21 CFR 807.87(l).

Intercenter Consultation Requests

The data in the table below reflects Intercenter Requests for Consultative or Collaborative Review forms received in OCP during this reporting period. These data are indicative of the number of premarket reviews of combination products that involved a consulting agency Center[9]. As indicated later in this report, educational efforts during this period focused on training Center review staff on the requirements of this new process. As the primary assigned Center, CBER requested 24 Intercenter Consultations (8 consultations with CDER, 16 consultations with CDRH), CDER requested 14 Intercenter Consultations (2 consultations with CBER, 12 with CDRH), and CDRH requested 43 intercenter consultations (3 with CBER, 40 with CDER).[10]

		Consulting Center		
		CBER	CDER	CDRH
Primary Assigned Center	CBER	---	8	16
	CDER	2	---	12
	CDRH	3	40	---

[9] Some applications were associated with multiple consulting requests. Additionally, since 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 since April 1, 2003, as reported in the previous section.

[10] During this initial start-up phase of this process, it is likely that not all intercenter requests for consultations were submitted to the Office of Combination Products for tracking and monitoring purposes. The Web-enabled database being developed to provide for electronic completion, monitoring, and tracking of combination products consult requests will automate this process and better ensure submission of all such requests to OCP. Educational efforts on the process and procedures for intercenter consult reviews will continue.

Activities and Impacts

OCP's FY 2003 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**. Responding to requests from both industry and agency review staff, OCP facilitated meetings and discussions at key milestones in the review process of particular marketing applications to ensure continued and consistent communication by the review staff, including clearly delineated regulatory paths for product approval. Additionally, OCP conducted post-approval debriefings with review staff and industry to share best practices and lessons learned. The practices and processes developed as a result of these actions will serve as models for the review of future submissions of similar products.
- **Provided support to Centers and sponsors**. OCP facilitated meetings and communications on a number of specific issues/products that contributed to ensuring the timely and effective review of these combination products. Examples included: determination of product classification (e.g., whether or not a product is a combination product); clarification of regulatory pathways and review timeframes; facilitating discussion of review processes and respective responsibilities of Centers involved in joint reviews; and suggested methods to simplify submission practices. Product specific issues involved a diverse array of combination products in product areas such as cardiovascular, anesthesiology, oncology, orthopedics, and radiology.
- **Formed and chaired an internal agency working group to establish reliable, reproducible mechanisms to simplify the premarket regulatory and submission process for combination products**. This group is comprised of experts from OCP, CBER, CDER, CDRH, and OCC. The team is considering the need for single vs. separate marketing applications, guiding principles for the selection of premarket regulatory authorities, and developing recommendations for the format and content of submissions for combination products.
- **Developed an OCP Intranet site under contract**. The site will ultimately provide agency reviewers access to an internal repository of information on the regulation of combination products.
- **Developed and implemented processes to fulfill MDUFMA's requirement that OCP report annually to Congress on the numbers and types of combination products under review**:
    - OCP worked with CBER, CDER, and CDRH to reach consensus on database requirements to provide for premarket submissions to be categorized as to whether or not they concern a combination product, and if so, what type. Effective April 1, 2003, (for CBER and CDER) and May 1, 2003, (for CDRH),

premarket submissions are being categorized as to whether or not they concern a combination product, and if so, what type.

- OCP developed an algorithm and categorization scheme for combination products in collaboration with the Centers and OCC to describe the types of combination products under review in the agency. 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 combined with a drug or biologic, a co-packaged product or kit, or separate products with mutually conforming labeling. OCP developed a Web-based decision support tool to facilitate use of the algorithm for reviewers and project managers. This internal tool is available on the OCP Intranet Web site.

OCP's FY 2003 activities and impacts related to the consultative/collaborative review process are as follows:

- **Revised the SOP on the Intercenter Consultative/Collaborative Review Process to provide for OCP monitoring and tracking of all consultation requests for combination products occurring between CBER, CDER, and CDRH.** The revisions were concurred with by the CBER, CDER, and CDRH Directors and implemented on February 14, 2003. The current version of the SOP is posted at http://www.fda.gov/oc/combination/consultative.html.
- **Established a mail courier system specifically designed to ensure the prompt delivery of regulatory submissions, consulting requests and reviews, and similar material between the Centers to facilitate the prompt review of combination products requiring intercenter consultations.**
- **Trained center review staff on the process and procedures for the new intercenter consultation process for combination products**.
- **Provided support to review staff to facilitate the intercenter consultation process**. Examples include identification of consulting divisions and contacts, clarification of due dates and completion status, and identification and resolution of barriers to timely completion of consultation requests.
- **Actively monitored the intercenter consultation process on combination products under review to ensure that the requesting Center received timely and constructive feedback**.
- **Explored avenues to modify Center time reporting mechanisms to include combination products in order to elevate the importance of timely intercenter consult reviews by providing credit to reviewers for time spent on this process**.
- **Began developing an internal, Web-enabled database that will provide for electronic completion, monitoring, and tracking of all consultation requests occurring between CBER, CDER, and CDRH**. This system will also be available for the Centers to use to track intra-Center consultative reviews.
- **Conducted a retrospective review of issues related to the successful completion of consults during the first and second quarters of 2003**. Surveyed Center reviewers and consult coordinators to obtain feedback and best practices for coordinating and conducting intercenter consults. Drafted reviewer tools with tips for successful intercenter consultations.

Consistent and Appropriate Postmarket Regulation

MDUFMA requires OCP to ensure the consistency and appropriateness of postmarket regulation of combination products. In general, a combination product is subject to the postmarket reporting requirements associated with the premarket regulatory path. This is the "default" position when the agency does not specifically exercise its discretion to apply features of the various regulatory authorities for a particular combination product. However, postmarket reporting requirements for some combination products may most appropriately be achieved by drawing from a mixture of regulatory authorities.

Activities and Impacts

OCP's FY 2003 activities and impacts related to the consistency of postmarket regulation are as follows:

- **Formed and chairs internal agency working groups to develop policy and guidance regarding the postmarket issues of most significance to our stakeholders (see "Additional FY 2003 Activities and Impacts" section).** These teams are developing guiding principles and processes to address the following issues:

    - *Manufacturing and Quality System Regulations*. The initial focus of this team has been to identify the similarities and differences between the Current Good Manufacturing Practice (cGMP, 21CFR 210 and 211) systems used for drugs and biologics and the Quality Systems Regulation (QSR, 21 CFR 820) used for devices. The group is considering various product/manufacturing scenarios and developing guiding principles for determining how cGMP and QSR authorities could be applied for combination products. This team has also worked on the development of processes to ensure appropriate communication between Centers on manufacturing/quality system requirements for combination products. Several members of this group are also working on the agency cGMPs for the 21st Century initiative.

    - *Adverse Event Reporting Regulations*. The initial focus of this team has been to develop internal procedures to ensure adequate intercenter communication of adverse experiences for combination products. The group also expects to develop policy for FDA and industry on the application of adverse event reporting regulations for combination products.

    - *Registration and Listing*. The focus of this working group has been to develop mechanisms to share registration and listing data across Centers for combination

products, and to provide industry with a clear, consistent approach for the listing of combination products where required.

- **Established a process to ensure appropriate communication and consultation between Center postmarket reviewers for a new type of drug-device product for which the agency expects to receive a significant number of applications**. This process will serve as a model for future products.

- **Expanded the information provided in assignment decision letters to provide sponsors with a better understanding of the scope of regulatory requirements for their products**. OCP letters have been expanded to provide the agency's preliminary determination of GMP and adverse event reporting requirements when such determinations can be made at the time of assignment.

- **Provided support to Centers or sponsors to ensure the consistency and appropriateness of postmarket regulation of combination products**. Examples include coordination of agency determination of whether product claims are supported or acceptable; ensuring manufacturing supplements are appropriately routed for review; facilitating follow-up between Centers on adverse event reports for combination products; and clarification of the selection of appropriate postmarket regulatory authorities.

Effective Resolution of Review Disputes

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

Performance

There have been no formal requests to resolve a dispute regarding the timeliness of a combination product review received during this reporting period. The "Timely and Effective Premarket Review" section of this report provides examples of informal facilitation and resolution of issues related to premarket review.

Activities and Impacts

A guidance document for recommended processes and procedures for submitting and resolving disputes regarding the timeliness of the premarket review of combination products is in development.

Additional FY 2003 Activities and Impacts

Additional activities and impacts of OCP in FY 2003 are as follows:

- **Launched OCP's Internet site** (http://www.fda.gov/oc/combination) **in March 2003.** The site was visited by over 3,000 unique users during the first month of operation alone. Content includes the following:
    - Quarterly progress reports to stakeholders on OCP activities (http://www.fda.gov/oc/combination/quarterlyrpts.html).
    - Information regarding the assignment of combination products (http://www.fda.gov/oc/combination/assignment.html).
    - A compilation of relevant guidance documents from CBER, CDER, and CDRH to aid sponsors seeking to develop combination products (http://www.fda.gov/oc/combination/guidance).
    - A list of significant new approvals linked to review documentation (when available) to inform sponsors about the regulatory pathways utilized for combination products (http://www.fda.gov/oc/combination/approvals).
    - Stakeholder perspectives on combination product issues presented at the November 25, 2002, public hearing (http://www.fda.gov/oc/combination/agenda.html).

- **Established an email address for internal and external inquiries** (combination@fda.gov).

- **Conducted 12 presentations to FDA staff and 11 presentations to external stakeholders for education, outreach, and training purposes.** Internal presentations were focused on raising awareness of combination product issues, providing training on the Intercenter Consultation Process, and the use of an algorithm and categorization scheme to determine whether or not a product is a combination product and which category best describes that combination product. External stakeholder presentations focused on the assignment and regulation of combination products, and OCP activities and initiatives.

- **Provided a variety of press interviews about combination product regulation and OCP roles and responsibilities.**

- **Participated in working groups to support the Commissioner's Technology Development Initiatives**. OCP is participating in the working groups established to clarify and develop the regulatory pathways for novel drug delivery systems and drug/test kit combination products based on pharmacogenomics. OCP is also participating in internal agency working groups being established to develop guidance documents for

products (some of which are combination products) for the treatment and diagnosis of diabetes and obesity.

- **Obtained input from Internal and External Stakeholders**:
    - A November 25, 2002, public hearing to solicit information and views on the issues and concerns relating to the assignment, premarket review, and postmarket regulation of combination products. Eleven presentations representing regulated industry and/or trade associations were made at the public hearing. Thirteen manufacturers and trade associations also submitted written comments to the docket. The comments were reviewed and considered by OCP working groups (e.g., manufacturing/quality systems, adverse event reporting, single versus separate applications) in the development of new policies and guidance. Working groups will also consider additional ways to obtain stakeholder input as new policies are developed.
    - Meetings with senior leadership in CBER, CDER, and CDRH to determine how OCP could best provide value added to the Centers' activities.