

# **FY 2014**

## ***PERFORMANCE REPORT TO CONGRESS***

*for the*

### ***Office of Combination Products***

*as required by the*

*Medical Device User Fee and  
Modernization Act of 2002*



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



## ***Acting Commissioner's Report***

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I am pleased to submit the Food and Drug Administration's (FDA or the Agency) Fiscal Year (FY) 2014 Annual Report to Congress for the Office of Combination Products (OCP). This report includes data from the 11<sup>th</sup> full year since OCP was established, as mandated by the Medical Device User Fee and Modernization Act of 2002, P.L. 107-250 (MDUFMA), enacted on October 26, 2002.

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

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

Combination products are likely to become more complicated as new technologies emerge and existing technologies mature. Therefore, OCP will continue to focus on the most important issues relating to the regulation of combination products. OCP is committed to actively assisting industry and FDA reviewers in understanding the complexities of this regulatory area.

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

Stephen M. Ostroff, M.D.  
Acting Commissioner of Food and Drugs

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## ***Executive Summary***

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FDA established the Office of Combination Products (OCP) on December 24, 2002, as required by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA). The statutory mission of OCP is to ensure the prompt assignment of combination products (for drug-device, biologic-device, drug-biologic, or drug-device-biologic products) to FDA Centers, the timely and effective premarket review of such applications, and consistent and appropriate postmarket regulation of these products, after approval.

OCP documented 760 activities in FY 2014.<sup>1</sup> The topics of these activities included jurisdiction/classification, premarket review, and postmarket regulation.

This document presents OCP's Annual Report to Congress and covers activities and accomplishments during FY 2014 (October 1, 2013-September 30, 2014). OCP's activities and performance for FY 2014 that are highlighted in this report include:

- **Prompt Assignment of Combination Products.** In FY 2014, OCP continued to clarify the jurisdictional assignment of combination products and to provide prompt Request for Designation (RFD) decisions. OCP issued 8 combination product RFD assignments with every assignment meeting the 60-day statutory decision time requirement. OCP also provided timely informal jurisdictional assistance for approximately 250 separate informal inquiries.
- **Timely and Effective Premarket Review.** In FY 2014, OCP continued to make significant contributions to the premarket review of combination products by responding to 650 requests for assistance from Centers and sponsors. This is a 67 percent increase from the 390 requests received in 2013. Other OCP activities relating to premarket review included chairing and/or participating in a number of working groups to examine regulatory issues, clarifying interpretive standards, addressing challenging categories of products, identifying and resolving specific product issues, and continuing to develop guidance documents explaining how FDA determines whether a product is a drug, device, biological product, or combination product.
- **Combination Product Review.** FDA received 310 original premarket applications for combination products in FY 2014. This is a 1 percent decrease from the 313 in FY 2013.<sup>2</sup> Inter-Center consulting reviews increased 22 percent to 1,013 for FY 2014 from 828 in FY 2013. Examples of approved combination products can be found at the OCP Web site [www.fda.gov/CombinationProducts/default.htm](http://www.fda.gov/CombinationProducts/default.htm).

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<sup>1</sup> Some of these reported activities may have involved more than one type of activity (e.g., premarket review issues and postmarket regulation issues) and may be represented and/or recorded as multiple types of activities. The activities reported do not include formal OCP activities (e.g., responses to RFD submissions).

<sup>2</sup> FY 2013 numbers were changed to reflect updates to data presented in the FY 2013 OCP Performance Report. The updated data for FY 2013 is located in Appendix A.

- **Consistent and Appropriate Postmarket Regulation.** In FY 2014, OCP provided clarification and support for 110 separate postmarket matters. OCP continued to chair two FDA working groups to address how current good manufacturing practices (CGMPs) apply to combination products, to work with other FDA components to clarify the requirements for postmarket safety reporting and registration and listing for combination products, and to update information technology systems for safety reports and listings for combination products. OCP also continued to work with the medical product Centers to resolve postmarket safety issues, registration and listing issues pertaining to specific combination products.
- **Additional Activities and Accomplishments.** OCP continued to conduct external outreach activities through a variety of educational and informational presentations to national and international audiences. These activities were intended to foster greater efficiency of the combination product development and premarket review process by enhancing understanding of the complex regulatory issues that arise regarding combination products.

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## **Acronyms**

**510(k)** – Premarket Notifications

**BLA** – Biologics License Application

**CBER** – Center for Biologics Evaluation and Research

**CDER** – Center for Drug Evaluation and Research

**CDRH** – Center for Devices and Radiological Health

**CFR** – Code of Federal Regulations

**CGMP** – Current Good Manufacturing Practice

**FDA** – Food and Drug Administration

**FY** – Fiscal Year (October 1 to September 30)

**HDE** – Humanitarian Device Exemption

**IDE** – Investigational Device Exemption

**IND** – Investigational New Drug

**ISO** – International Organization for Standardization

**MDUFA** – Medical Device User Fee Amendments of 2007

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

**NDA** – New Drug Application

**NSE** – Not Substantially Equivalent

**OCC** – Office of the Chief Counsel

**OCP** – Office of Combination Products

**PDUFA** – Prescription Drug User Fee Act

**PMA** – Premarket Approval Application

**PMC** – Postmarketing Commitment

**PMR** – Postmarketing Requirement

**RFD** – Request for Designation

**SE** – Substantially Equivalent

## ***Introduction***

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On October 26, 2002, Congress enacted MDUFMA. Among other things, MDUFMA required FDA to establish an office “to ensure the prompt assignment of combination products to agency centers, the timely and effective premarket review of such products, and consistent and appropriate postmarket regulation of” combination products. In response, FDA established OCP within the Office of the Commissioner. Information about OCP, including the authorizing text of MDUFMA, can be found at the OCP Web site at [www.fda.gov/CombinationProducts/default.htm](http://www.fda.gov/CombinationProducts/default.htm).

### **Description of Combination Products**

Combination products are developed to enhance the safety and effectiveness of non-combination medical products. Combination products are those identified in Title 21 Code of Federal Regulations (CFR) § 3.2(e):

- (1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that is physically, chemically, or otherwise combined or mixed and produced as a single entity;
- (2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
- (3) A drug, device, or biological product packaged separately that, according to its investigational plan or proposed labeling, is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or,
- (4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Combination products have the potential to provide enhanced therapeutic advantages compared to non-combination devices, drugs, and biologics and incorporate cutting-edge, novel technologies that hold great promise for advancing patient care. Combination products may include drug-delivery systems, gene therapy systems, personalized medicine drug-device combinations, biological-device combinations, nanotechnology, and other innovative products for diagnostic and therapeutic treatment of cardiovascular, neurological, metabolic, oncologic, and other disorders.

## **Statutorily Mandated Functions of OCP**

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 duties relating to premarket review and postmarket oversight for these products. However, the primary responsibilities for scientific premarket review and postmarket regulation of combination products remain in one of the three medical product Centers – CBER, CDER, or CDRH – to which they are assigned by OCP. Specifically, section 503(g)(4)(B-F) of the Federal Food, Drug, and Cosmetic Act requires OCP to, among other things:

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

Among other activities, OCP serves as a focal point for addressing combination product issues raised by FDA reviewers and industry and works with the relevant Centers to develop guidance documents and regulations to clarify the regulation of combination products.

In addition, OCP has responsibility for FDA action on all RFDs submitted by industry in accordance with 21 CFR Part 3, “Product Jurisdiction.” This responsibility includes responding to requests for classification of a particular product as a biological product, device, or drug, or combination product, as well as requests for product assignment.

## Performance Presented in This Report

This section includes FY 2014 OCP activities and accomplishments in the assignment of combination products and in coordinating the premarket review and postmarket regulation of combination products. OCP also is required to provide an annual review performance assessment for the various combination product applications. Accordingly, this section also provides performance information for FY 2014 and updates FY 2013 performance information for reporting timeliness in days of the reviews of combination products in the subsection “Timely and Effective Premarket Review.”

Consistent with the mandated functions of OCP, information in this section presents information and data on OCP activities related to:

- Prompt assignment of combination products
  - Timeliness of the assignment of combination products
- Timely and effective premarket review
  - Number and types of combination products under review
  - Timeliness of the reviews of combination products
  - Number of premarket reviews of combination products that involved a consulting Center
- Consistent and appropriate postmarket regulation
- Effective resolution of review disputes
  - Timeliness of dispute resolutions regarding combination products

Unless otherwise noted, all performance data in this section are as of September 30, 2014.

## **Prompt Assignment of Combination Products**

OCP is required to assign premarket review responsibility for combination products based on the product's primary mode of action (PMOA) or assignment algorithm (see 21 CFR 3.4(b)) within 60 days of filing a RFD.

### **Requirement Workload Trends: FY 2009 to FY 2014**

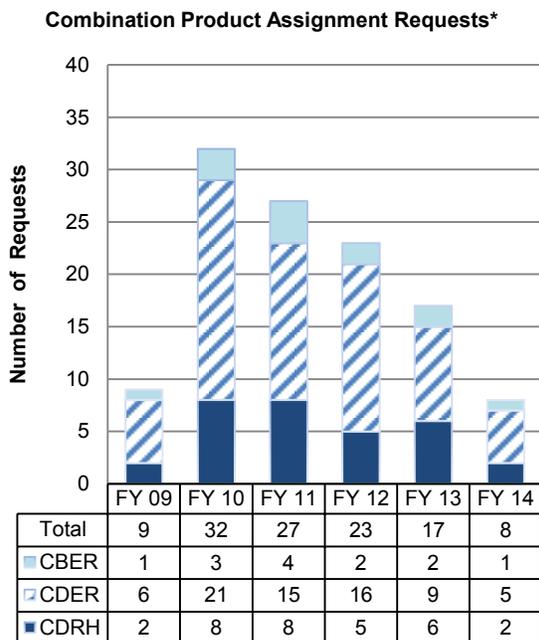
Review workloads in FY 2014 are compared to the previous 5-year averages for the total number of combination product assignment requests and the total number of non-combination product classifications and assignment requests in the table below. Review workloads for both types of assignments are down compared to their respective 5 year averages. Specifically, total formal combination product classifications and assignments are down 64 percent in FY 2014 and non-combination classifications and assignments are also down 18 percent for FY 2014 compared to their respective 5 year averages.

**OCP Requirement Workloads**

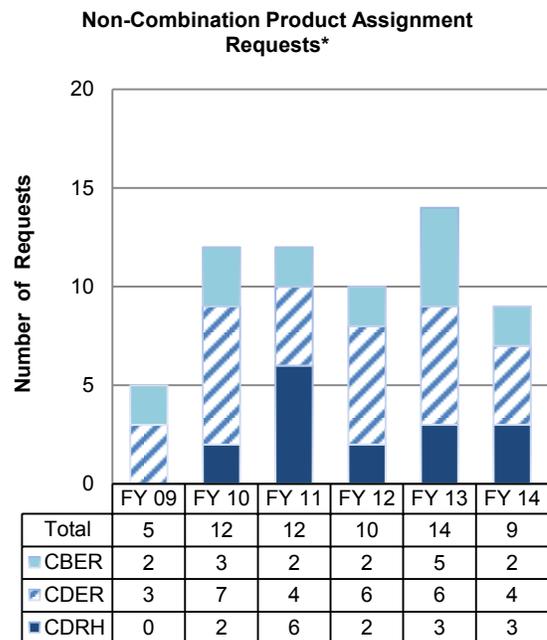
<b>Submission/Request</b>	<b>FY 09</b>	<b>FY 10</b>	<b>FY 11</b>	<b>FY 12</b>	<b>FY 13</b>	<b>FY 14</b>	<b>FY 09 to FY 13 5-Year Average</b>	<b>FY 14 Compared to 5-Year Average</b>
Total Formal Combination Product Classifications/ Assignments	9	32	27	23	17	8	22	- 64%
Total Formal Non-Combination Product Classifications/ Assignments	5	12	12	10	14	9	11	- 18%

The total number of formal combination product classifications and assignments issued continued to decrease in FY 2014 to the lowest number in the past 5 years.

The total number of formal product classifications and assignments for non-combination products decreased in FY 2014 to the lowest number since FY 2009, driven by decreases in CBER and CDER assignment requests.



\*Totals are the number of requests by the requesting Centers.



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RFD workload is based on 63 RFD submissions that were received during FY 2014 and four RFD submissions that were carried over from FY 2013 (pending and not overdue as of October 1, 2013) for a total of 67 RFD submissions under consideration. Of these 67 RFD submissions under consideration during FY 2014, decisions were issued for 17 submissions (25 percent), 46 RFD submissions were found by OCP to have insufficient information for filing (69 percent), and 4 submissions were withdrawn by the sponsor prior to issuance of a decision (6 percent).

## FY 2014 Review Performance

In FY 2014, 17 formal assignment requests were issued for combination and non-combination products, all within the 60-day review time goal (see tables on the following page). The combination product assignment times ranged from 41 to 60 days, with a median product assignment time of 58 days. The non-combination product assignment times ranged from 31 to 60 days, with a median product assignment time of 50 days. Of the 17 assignment decisions in FY 2014, 8 were identified as combination products and were issued within the goal timeframe.

**Workload for Number of Combination Product Assignments Issued**

Determination	Product Assignments Issued*	Percent On Time*
Drug-Device	5	100%
Drug-Biologic	1	100%
Device-Biologic	0	100%
Drug-Device-Biologic	2	100%
<b>Total</b>	<b>8</b>	<b>100%</b>

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

**Workload for Number of Non-Combination Product Assignments Issued**

Determination	Product Assignments Issued*	Percent On Time*
Drug	3	100%
Biologic	3	100%
Device	3	100%
<b>Total</b>	<b>9</b>	<b>100%</b>

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

**OCP Requirements and Accomplishments**

Type of Activity	FY 2014 Accomplishments
<b>Issuing required assignments within 60 days</b>	OCP issued all required assignments within 60 days. If OCP does not provide a written response within sixty days, the sponsor's recommendation respecting the classification of the product is considered to be the final determination.
<b>Responding to 248 stakeholder informal inquiries</b>	OCP responded to 248 informal stakeholder inquiries related to product classification and jurisdiction assignment, primarily by e-mail and telephone. This represents a 6 percent increase in informal inquiries for classification and jurisdictional assignment compared to FY 2013.
<b>Clarifying standards for product classification and prepare guidance on this issue</b>	OCP continued to chair a working group including staff from CDER, CDRH, CBER, and the Office of Chief Counsel (OCC), to clarify interpretive standards, address classification and assignment of challenging categories of products, and pursue related policy initiatives, including developing guidance on how FDA determines whether a product is a drug, device, biological product, or combination product, and to clarify standards for cross-labeled combination product status. OCP also participated in an FDA working group developing guidance to clarify classification criteria for human tissue products.
<b>Enhancing the timeliness, consistency, and clarity of jurisdictional decisions across FDA</b>	OCP continued to facilitate monthly product jurisdictional meetings to exchange information between OCP jurisdictional and assignment specialists, jurisdictional officers from CBER, CDER, and CDRH, and attorneys from OCC. OCP continued to provide training to review staff including Office of Regulatory Affairs inspectors on standards for classification and assignment of combination products, to facilitate identification of products that may raise jurisdictional or inspectional questions.

## ***Timely and Effective Premarket Review***

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OCP is responsible for ensuring the timely and effective premarket review of combination products, including by overseeing the timeliness of reviews and coordinating reviews involving more than one Center. In 2002, FDA established policies and procedures for FDA staff to follow when requesting, receiving, handling, processing, and tracking formal reviews of combination products, devices, drugs, and biologics. This policy was formally incorporated into the FDA Staff Manual Guide, Agency Program Procedures, Volume IV, effective June 18, 2004, and is available on the FDA Web site at

[www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm135860.htm](http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm135860.htm).

### **Number and Types of Combination Products under Review**

FDA is required to report the number and types of combination products under review. The following information refers to FDA performance presented in this subsection.

- The number and types of combination products under review for FY 2014 by CBER, CDER, and CDRH included submissions filed or received in FY 2014. The number of combination product submissions is a small subset of the total number of submissions received by FDA.
- When reporting timeliness in days of the review for CBER-led or CDER-led combination products, Prescription Drug User Fee Act (PDUFA V) goals were referenced for priority and standard new drug applications (NDAs) and biologics license applications (BLAs). With CBER-led or CDRH-led combination products, MDUFA III goals were referenced for expedited and original premarket approval applications (PMAs), premarket notifications [510(k)s], and device BLAs. Performance goals apply to only a subset of applications of a certain type. Therefore, not every application is required to be reviewed in accordance with a user fee-related time frame.
- Some product review goals, such as for NDAs, are defined by number of months. Due to the differences in the numbers of days in each month (28 to 31), 10 months represents a range from 303 days (such as February 1 to December 1) to 306 days (such as March 15 to January 15), and 6 months represents a range from 182 days (such as February 15 to August 15) to 184 days (such as July 15 to January 15).
- Median review time was based on FDA first cycle review performance for PDUFA V goals. For MDUFA III goals, median review times were based on total MDUFA III decision review time. Actual review time was used when only one action was measured.

## Requirement Workload Trends: FY 2009 to FY 2014

Review workloads in FY 2014 are compared to the previous 5-year averages for the total combination products submitted for review and the total inter-Center consult requests in the table below.

### OCP Requirement Workloads

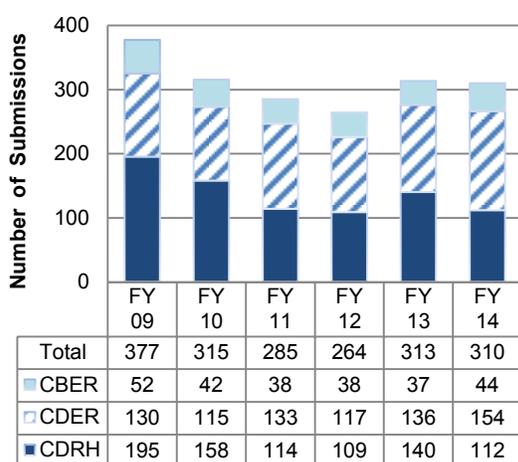
Submission/Request	FY 09	FY 10	FY 11	FY 12	FY 13*	FY 14	FY 09 to FY 13 5-Year Average	FY 14 Compared to 5-Year Average
Total Combination Products Submitted for Review	377	315	285	264	313*	310	311	+ 0%
Total Inter-Center Consult Requests	455	466	530	660	828	1,013	588	+ 72%

\* FY 2013 numbers were changed to reflect updates to data presented in the FY 2013 OCP Performance Report.

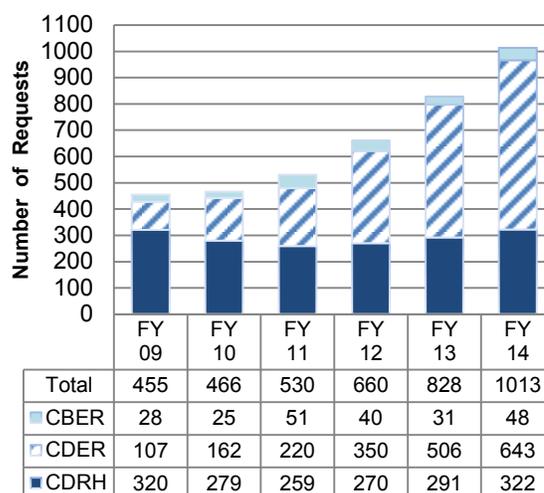
The total number of combination products submitted for review in FY 2014 was approximately the same as 2013. Fifty percent of the combination product application submissions received and categorized related to CDER, followed by CDRH (36 percent) and CBER (14 percent).

The total number of inter-Center consult requests continued to increase in FY 2014 to the highest number in five years, driven by a consistent increase in consultation requests from CDER.

**Combination Product Application Submissions**



**Inter-Center Consultation Requests**



FDA is required to report the number of premarket reviews of combination products that involved a consulting Center. The table below reflects the number of forms received and monitored by OCP requesting inter-Center requests for consultative or collaborative reviews during FY 2014, broken down by primary assigned Center and which Center requested the consult.<sup>3</sup>

**Number of Premarket Reviews of Combination Products  
Involving Requests for Inter-Center Consulting**

<b>Primary Assigned Center</b>	<b>CBER Consulting</b>	<b>CDER Consulting</b>	<b>CDRH Consulting</b>	<b>Number of Consults</b>
CBER	--	8	40	48
CDER	7	--	636	643
CDRH	4	318	--	322
<b>Total</b>	<b>11</b>	<b>326</b>	<b>676</b>	<b>1,013</b>

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<sup>3</sup> 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 2014, as reported in the previous section.

The table below reflects 310 original applications for NDAs, BLAs, PMAs, 510(k)s, investigational new drugs (INDs), investigational device exemptions (IDEs), and humanitarian device exemptions (HDEs) initially classified into one of nine categories of combination products received in FY 2014. The same table reflecting applications received in FY 2013 is updated in Appendix A to reflect corrections and actions as of September 30, 2014. The majority of the applications (51 percent) were Original INDs, followed by Original 510(k)s (21 percent) and Original IDEs (17 percent). The most common combination product category was a device coated/impregnated/otherwise combined with a drug (22 percent), followed by a pre-filled drug delivery device/system (21 percent).

#### Workload by Combination Product Category Number

Application Type	1	2	3	4	5	6	7	8	9	Totals
Original NDAs	3	14	0	0	0	0	0	0	1	18
Original BLAs	0	0	5	0	0	0	0	0	6	11
Original PMAs	0	0	0	3	0	0	2	0	1	6
Original 510(k)s	4	0	0	33	6	1	4	7	9	64
Original INDs	12	50	18	12	1	32	2	28	4	159
Original IDEs	0	0	0	19	3	0	22	6	2	52
Original HDEs	0	0	0	0	0	0	0	0	0	0
<b>Totals</b>	<b>19</b>	<b>64</b>	<b>23</b>	<b>67</b>	<b>10</b>	<b>33</b>	<b>30</b>	<b>41</b>	<b>23</b>	<b>310</b>

**Combination Product Category Key:**

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>1 = convenience kit or co-package</li> <li>2 = pre-filled drug delivery device/system</li> <li>3 = pre-filled biologic delivery device/system</li> <li>4 = device coated/impregnated/otherwise combined with drug</li> <li>5 = device coated or otherwise combined with biologic</li> </ul> | <ul style="list-style-type: none"> <li>6 = drug/biologic combination</li> <li>7 = separate products requiring mutually conforming labeling</li> <li>8 = possible combination based on mutually conforming labeling of separate products</li> <li>9 = other type of combination product</li> </ul> |
|--|---|

## Timeliness in Days of the Reviews of Combination Products

FDA is required to report the timeliness in days of the reviews of combination products. The table below summarizes the review type and review performance target for original NDAs, BLAs, PMAs, and 510(k)s. PDUFA V and MDUFA III established review performance goals for many types of drug, device, and biological product premarket applications. These goals reflect current expectations about the portion of premarket applications that will be reviewed within a specified time frame. Performance goals apply to only a portion of all applications of a certain type, and they do not require that every application be reviewed in accordance with the applicable time frame. Typical goals range from 50 percent to 90 percent and vary by year. For MDUFA III performance goals, refer to [www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM295454.pdf](http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM295454.pdf).

For PDUFA V performance goals, refer to [www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf](http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf).

**Performance Goals for Original Applications<sup>†</sup>**

User Fee Act	Original Application Type	Review Type	Review Within
PDUFA V	NDAs	Priority	6 months
PDUFA V	NDAs	Standard	10 months
PDUFA V	BLAs	Priority	6 months
PDUFA V	BLAs	Standard	10 months
MDUFA III	Expedited and Original PMAs	Decision for PMA Filed Submissions with no Advisory Committee Input	180 days
MDUFA III	Expedited and Original PMAs	Decision for PMA Filed Submissions with Advisory Committee Input	320 days
MDUFA III	510(k)s	SE or NSE decision*	90 days
MDUFA III	BLAs	Priority	6 months
MDUFA III	BLAs	Standard	10 months

\* Substantially equivalent (SE) or not substantially equivalent (NSE)

<sup>†</sup> The timelines to take action for BLAs that fall under the MDUFA III timeline are 6-months from receipt for a priority review and 10-months for a standard review. The timelines for NMEs and BLAs that fall under PDUFA V's "Program" Review Model are 10-months for standard applications and 6-months for priority reviews from the 60-day filing date (or 12 months and 8 months respectively from the date of submission of the application) input.

FDA review performance information, with respect to premarket review, for CBER, CDER, and CDRH is based on a fiscal year receipt cohort. This methodology calculates performance information for submissions for the fiscal year FDA received them, regardless of when FDA acted on or approved the submissions. This section updates FDA's review performance on the FY 2013 combination product submissions and presents FDA's review performance on the FY 2014 combination product submissions through September 30, 2014.

## FY 2013 and FY 2014 Review Performance

Final FY 2013 review goal performance is presented in the table below.

Original Application Type	Review Type	Review Within	Number of Combination Products*	Median or Actual Review Time (Days)	Range of Review Time (Days)
NDA	Priority	6 months	2	207	174 to 239
NDA	Standard	10 months	15	304	299 to 385
BLA	Priority	6 months	1	334	334
BLA	Standard	10 months	4	411	304 to 456
Expedited and Original PMAs	FDA Decision	180 or 320 days <sup>†</sup>	3	116	99 to 180
510(k)s	SE or NSE decision	90 days	73	58	8 to 113

\* FY 2013 numbers were changed to reflect updates to data presented in the FY 2013 OCP Performance Report.

<sup>†</sup> Review within 180 days for decisions without Advisory Committee Input and review within 320 days for decisions with Advisory Committee input.

Preliminary FY 2014 review goal performance is presented in the table below.

Original Application Type	Review Type	Review Within	Number of Combination Products	Median or Actual Review Time (Days)	Range of Review Time (Days)
NDA	Priority	6 months	2	104	104
NDA	Standard	10 months	15	304	304
BLA	Priority	6 months	0	0	0
BLA	Standard	10 months	4*	0	0
Expedited and Original PMAs	FDA Decision	180 or 320 days <sup>†</sup>	5	180	86 to 318
510(k)s	SE or NSE decision	90 days	56	81	20 to 147

\* Included in this count are BLAs that are pending filing since the assumption is that they will go on to be filed. These are preliminary numbers that may change if reporting filed figures differ from receipt figures.

<sup>†</sup> Review within 180 days for decisions without Advisory Committee Input and review within 320 days for decisions with Advisory Committee input.

## OCP Requirements and Accomplishments

### Premarket Review Process

OCP continued to facilitate the premarket review processes for combination products having complex regulatory issues. OCP fosters early interactions between industry and FDA to develop clearly delineated regulatory pathways for the development and expeditious review of premarket submissions for combination products. Responding to requests from both industry and FDA review staff, OCP consults and provides guidance on unique regulatory issues presented by combination products such as the number of marketing applications, labeling requirements, human factor testing and pre-clinical testing requirements. OCP also leads or participates in meetings and discussions to ensure continued and consistent communication between sponsors and FDA review staff. OCP FY 2014 accomplishments related to premarket review are included in the table below.

Type of Activity	FY 2014 Accomplishments
<b>Developing regulations</b>	OCP published a final rule in January 2013 intended to promote the public health by clarifying which CGMP requirements apply when drugs, devices, and biological products are combined to create combination products (see 21 CFR Part 4). In 2014, OCP chaired a working group to develop guidance for industry related to the final rule and to augment associated training materials for investigators and compliance staff. This guidance and enhanced training is intended to facilitate timely, effective premarket review of combination products subject to premarket authorization by FDA. OCP is also an active member of the Association for the Advancement of Medical Instrumentation (AAMI) - TIR (Technical Information Report) 48 cGMP Combination Products Committee. In response to the finalization of the CGMP rule, the AAMI committee was focused on development of TIR 48 targeted to combination products manufacturers to help outline best practices with respect to CGMP obligations.
<b>Responding to 650 requests for assistance from Centers and sponsors relating to premarket review issues<sup>4</sup></b>	OCP received 650 requests for assistance, addressing a number of specific issues that contributed to ensuring the timely and effective review of combination products. OCP continued to address several broad review issues related to novel drug or biological delivery systems, in-vitro diagnostics, pharmacogenomics, photodynamic therapy, wound healing products, generic drugs that include devices, product-specific alignment of drug and device labeling, and development considerations for electronic cigarettes.
<b>Developing possible regulatory pathways for new products intended to be used with another sponsor's already-approved product</b>	OCP continued to work with the Centers and OCC on a product-specific basis to develop appropriate approaches to resolve the difficult and complex legal and public health issues associated with 1) determining the appropriate type of marketing application, 2) cross-labeling of combination products, and 3) non-combination products for general or class use.

<sup>4</sup> The number of premarket activities reported in this section includes the stakeholder informal inquiries reported above. This is because generally product classification and jurisdictional determinations are also premarket activities.

Type of Activity	FY 2014 Accomplishments
<b>Chairing or participating in inter-Center working groups to clarify issues related to combination products</b>	OCP chaired and participated in inter-Center working groups to develop policies and technical guidance on topics that include: biological product and tissue issues, product labeling, wound care, inter-Center compliance and other review processes, combination product drug shortage concerns, and human factors considerations. OCP participated in center working groups such as FDA's Task Force on Antimicrobial Resistance.
<b>Serving as a resource for FDA staff on the appropriate use and interpretation of the combination product categorization algorithm and associated categories</b>	All premarket applications in CBER, CDER, and CDRH were categorized as to whether they concern a combination product, and if so, what type.

### Consultative/Collaborative Review Process

OCP oversees inter-Center consults to ensure that review of premarket applications are completed in a timely manner and meet PDUFA V and MDUFA III timelines. Specifically, OCP tracks and monitors all ongoing inter-center consult requests; clarifies internal operating procedures, roles, and responsibilities; identifies consulting divisions and contacts; clarifies due dates and completion status; facilitates access to review documents; and responds to industry inquiries. Other areas of OCP involvement, on a less routine basis, include clarifying the impact of goal differences under PDUFA V and MDUFA III and resolving barriers to timely completion of consultation requests.

In addition to providing general consult process assistance and facilitating inter-Center communication, OCP also provided assistance to the Centers in resolving regulatory and scientific issues relating to specific combination products and to specific categories of combination products during FY 2014.

Type of Activity	FY 2014 Accomplishments
<b>Consultative/Collaborative Review Process</b>	<ul style="list-style-type: none"> <li>• Actively tracking, monitoring, and following up on a total of 1,013 inter-Center consult requests on combination products under review to ensure the requesting Center received timely and constructive feedback. Additional information on consult requests by Center is presented further in this section of the report.</li> </ul>
<b>Providing Significant Facilitation or Assistance</b>	<ul style="list-style-type: none"> <li>• Novel drug-device cancer therapies</li> <li>• Injector delivery systems (including intrathecal systems)</li> <li>• Traditional products with novel combination uses</li> <li>• Medical imaging drugs and devices</li> <li>• Coordination of premarket CGMP inspections</li> <li>• Data safety board issue development</li> <li>• Import-export of combination products or their constituent parts</li> <li>• Inter-Center compliance and safety evaluator processes for premarket evaluation and postmarket safety matters</li> <li>• Registration and listing and associated information technology considerations</li> </ul>

Type of Activity	FY 2014 Accomplishments
	<ul style="list-style-type: none"> <li>• Regulatory considerations for monograph drugs for use with a device constituent part</li> <li>• Risk determination and need for investigational application assessments</li> <li>• Unique device identifiers and standardized numerical identification</li> <li>• Technical evaluation of Critical Path proposal</li> <li>• Application of IND and IDE requirements for combination products</li> <li>• Application of user and facility fees to combination products</li> <li>• CDRH development of guidance on premarket regulation of drug-eluting stents</li> <li>• OCP also continues to chair the inter-center working group to develop solutions for ensuring labeling consistency between imaging drugs and imaging devices</li> </ul>
<p><b>Consultative/Collaborative Review Process</b></p>	<ul style="list-style-type: none"> <li>• OCP chairs an Intercenter working group to clarify the use of human factors studies to optimize combination product development.</li> <li>• OCP chairs an Intercenter working group to revise and enhance the Intercenter consult process.</li> <li>• OCP chairs a working group regarding container/closures and drug delivery devices.</li> </ul>

## **Consistent and Appropriate Postmarket Regulation**

OCP is tasked with ensuring the consistency and appropriateness of postmarket regulation of combination products. OCP meets this requirement by undertaking a variety of compliance-related and postmarket activities to help ensure the safety and quality of combination products. The compliance-related and postmarket activities include leading agency efforts to develop and publish regulations and guidance for postmarket safety and CGMPs for combination products, coordinating and overseeing FDA actions relating to novel and complex postmarket safety issues and CGMP compliance questions, and facilitating and leading meetings between industry and FDA regarding these matters. Settings for these activities include providing support to FDA field inspectors for products seized at ports of entry to stop illegal products from entering the United States, responding to product defect issues, providing guidance on enforcement issues relating to import requirements, and providing warning letter review. OCP FY 2014 accomplishments related to the consistency and appropriateness of postmarket regulation are included in the table below.

<b>Type of Activity</b>	<b>FY 2014 Accomplishments</b>
<b>Providing clarification and support on separate postmarket matters to ensure consistent and appropriate postmarket regulation of combination products</b>	OCP addressed 110 postmarket-related matters involving such issues as the application of CGMPs and quality system regulations for inspections of combination products, appropriate mechanisms and manufacturer responsibilities for reporting adverse events, and requirements for registration and listing.
<b>Developing regulations</b>	OCP published a proposed rule in FY 2009 to clarify the postmarketing safety reporting requirements for combination products. In FY 2014, OCP worked with OCC on clearance of a final rule, and with Centers to update IT systems to support tracking, sharing and assessment of safety reports for combination products.
<b>Guidance development</b>	OCP chaired a working group to develop guidance and augment training materials for CGMPs for combination products (see Timely and Effective Premarket Review section of this report on page 7).
<b>Procedures development</b>	Safety signals for combination products are submitted to CBER, CDER, and CDRH. OCP promoted consistency in the evaluation of adverse events and resolution of postmarket safety issues through coordination efforts and provision of regulatory guidance.

## ***Effective Resolution of Review Disputes***

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When requests are received, OCP is required to resolve disputes regarding the timeliness of the premarket review of a combination product. OCP facilitates communications between sponsors and FDA review staffs to identify, clarify, and resolve specific concerns associated with review timeliness. The facilitation of issues helps prevent the need for more formal dispute resolution.

### **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 2014. This was the eleventh consecutive year in which no formal requests were received. The “Timely and Effective Premarket Review” section of this report provides examples of informal facilitation and resolution of issues related to premarket review.

## ***Additional Activities and Accomplishments***

OCP formally documented activities performed during FY 2014. These are summarized in the table below. The Postmarket Regulations Issues increased by 108 percent in FY 2014 compared to the 5-year average.

**Number of OCP Documented Activities\***

<b>OCP Activities</b>	<b>FY 09</b>	<b>FY 10</b>	<b>FY 11</b>	<b>FY 12</b>	<b>FY 13</b>	<b>FY 14</b>	<b>FY 09 to FY 13 5-Year Average</b>	<b>FY 14 Compared to 5-Year Average</b>
Total Activities by Stakeholder	561	641	682	756	603	760	649	+ 17%
<i>Total Activities by Issue Type</i>								
Jurisdiction/Classification Assignments <sup>5</sup>	256	303	265	268	233	248	265	- 6%
Premarket Review Issues	423	551	495	388	390	650	449	+ 45%
Postmarket Regulation Issues	58	60	57	33	57	110	53	+ 108%

\* Some of these reported activities may have involved more than one type of activity (e.g., premarket review issues and postmarket regulation issues) and may be represented and/or recorded as multiple types of activities.

In addition to the required functions noted previously, OCP actively pursues strategies intended to further program objectives internally and externally. Although not exhaustive of all of OCP's supplemental activities, the information below highlights additional FY 2014 OCP accomplishments with regard to two categories of efforts: external outreach and regulatory initiatives.

### **External Outreach**

OCP conducts outreach activities to share information on FDA assignment and regulation of combination products by meeting with trade associations and coalitions (e.g., Combination Products Coalition, Advanced Medical Technology Association, Association for Advancement of Medical Instrumentation) representing the drug, device, biological product, and combination product industries, and participating in industry conferences. Discussions and presentations focus on a wide range of topics, including emerging issues in combination product regulation, the role of OCP, policies and guidances under consideration, rulemaking, companion

<sup>5</sup> The jurisdiction/Classification Assignments category listed in the table is a subset of the larger Premarket Review Issues category. As such, the Total Activities by Stakeholder represents the sum of the Premarket Review Issues and Postmarket Regulation Issues categories.

diagnostics, injector clinical development options, standards, and future industry needs. Examples of FY 2014 outreach activities are included in the tables on the following pages.

Type of Activity	FY 2014 Accomplishments
<p><b>Presentations and outreach activities</b></p>	<p>OCP participated in a number of outreach activities. The following are examples of some notable venues/events for which OCP provided presentations and/or educational outreach:</p> <ul style="list-style-type: none"> <li>• Regulatory/Affairs Professionals Society conference</li> <li>• BIOMEDevice Conference</li> <li>• FDA/Xavier University MedCon Medical Device Conference</li> <li>• Association for the Advancement of Medical Instrumentation/FDA International Conference on Medical Device Standards and Regulation</li> <li>• Drug Information Association Third Annual Conference on Combination Products</li> <li>• Parenteral Drug Association/FDA Joint Regulatory Conference</li> <li>• Medical Device Manufacturers Association</li> <li>• Informa Annual Conference on Combination Products</li> </ul>
<p><b>Published articles</b></p>	<p>OCP staff published an article that discussed considerations for marketing combination products. The publication is available at <a href="http://www.globalregulatorypress.com/features/browse_issues_may14en.shtml">www.globalregulatorypress.com/features/browse_issues_may14en.shtml</a>.</p>

## Regulatory Initiatives

OCP activities include efforts to assist in advancing initiatives important to and affecting the regulation of combination products. Examples of regulatory activities pursued in FY 2014 are included in the following table.

Type of Activity	FY 2014 Accomplishments
<p><b>Continuing to contribute to the advancement of innovative products initiatives</b></p>	<p>OCP assisted in determining the appropriate regulatory pathway for novel technology diagnostics and biomarkers under review for use with drug or biological products. OCP also continued to participate in the Intra-agency FDA Task Force on Nanotechnology and other nanotechnology-related activities. In addition, OCP worked with the Center for Tobacco Products, CDER, CDRH, and other FDA components on classification issues relating to e-cigarettes and products that include tobacco, drugs, and devices. OCP participated on working groups chaired by Centers to clarify common issues such as nomenclature for single patient use products and for novel package types. OCP provided assistance on combination products considerations for guidance and regulations developed by Centers on topics including development and premarket review of drug-eluting stents and unique identifiers for devices and combination products that include them. OCP coordinated development of consistent trial designs for certain novel cancer chemotherapeutic dedicated delivery systems.</p>
<p><b>Continuing to actively participate in the FDA Enterprise Initiatives and the development of requirements on drug and device registration and listing</b></p>	<p>OCP continued to serve as liaison to several FDA-wide electronic database initiatives with the goal of enhancing the infrastructure necessary to facilitate the safety and effectiveness of combination products and development of FDA-wide medical product databases applicable to combination products.</p>

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## Appendix

### Appendix A: FY 2013 Updated Performance Detail

The table below reflects 313 original applications for NDAs, BLAs, PMAs, 510(k)s, INDs, IDEs, and HDEs initially classified into one of nine categories of combination products received in FY 2013.

**Workload by Combination Product Category Number**

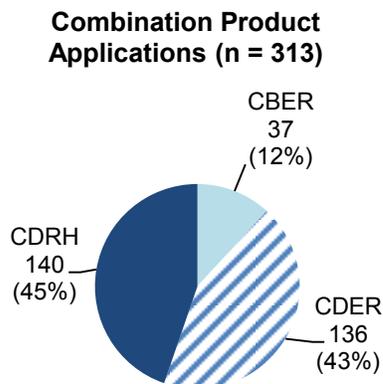
Application Type	1	2	3	4	5	6	7	8	9	Totals
Original NDAs	3	10	0	0	0	1	2	0	1	17
Original BLAs	0	0	5	0	0	0	0	0	0	5
Original PMAs	0	0	0	0	0	0	2	0	0	2
Original 510(k)s	4	0	0	54	3	0	1	2	10	74
Original INDs	27	35	15	5	6	30	3	21	8	150
Original IDEs	1	0	0	23	3	0	28	8	2	65
Original HDEs	0	0	0	0	0	0	0	0	0	0
<b>Totals</b>	<b>35</b>	<b>45</b>	<b>20</b>	<b>82</b>	<b>12</b>	<b>31</b>	<b>36</b>	<b>31</b>	<b>21</b>	<b>313</b>

**COMBINATION PRODUCT CATEGORY KEY:**

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

### Workload by Center Lead

The pie chart to the right shows the number and percentage of combination product applications in FY 2013 by Center lead, as of September 30, 2014.





**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, the 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  
Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20993-0002  
Phone: 301-796-4850

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the OCP Home Page at: [www.fda.gov/CombinationProducts/default.htm](http://www.fda.gov/CombinationProducts/default.htm).