FY 2015

PERFORMANCE REPORT TO CONGRESS

for the

Office of Combination Products

as required by the

Medical Device User Fee and Modernization Act of 2002

Food and Drug Administration
Department of Health and Human Services

Commissioner's Report

I am pleased to submit the Food and Drug Administration's (FDA or the Agency) Fiscal Year (FY) 2015 Annual Report to Congress for the Office of Combination Products (OCP). This report includes data from the 12th 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.

Robert M. Califf, M.D.
Commissioner of Food and Drugs

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Executive Summary

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.

This document presents OCP's Annual Report to Congress and covers activities and accomplishments during FY 2015 (October 1, 2014-September 30, 2015). OCP's activities and performance for FY 2015 that are highlighted in this report include:

- **Prompt Assignment of Combination Products**. In FY 2015, OCP continued to clarify the jurisdictional assignment of combination products and to provide prompt Request for Designation (RFD) decisions. OCP issued 2 combination product and 7 non-combination product RFD decisions with every assignment meeting the 60-day statutory decision time requirement. OCP also provided timely informal jurisdictional assessments for 139 separate informal inquiries.[1]

- **Timely and Effective Premarket Review**. In FY 2015, OCP continued to make significant contributions to the premarket review of combination products by responding to 700 requests for assistance from Centers and sponsors. This is an 8 percent increase from the 650 requests received in 2014. Other OCP activities relating to premarket review included chairing and/or participating in a number of working groups to examine regulatory issues and process improvement, clarifying interpretive standards, addressing challenging categories of products, identifying and resolving specific product issues, and the premarket review process and development considerations for combination products.

- **Combination Product Review**. FDA received 350 original premarket applications for combination products in FY 2015. This is a 10 percent increase from the 317 in FY 2014.[2] Inter-Center consulting reviews for combination products decreased to 932 for FY 2015 from 1,013 in FY 2014. Examples of approved combination products can be found at the OCP Web site www.fda.gov/CombinationProducts/default.htm.

- **Consistent and Appropriate Postmarket Regulation**. In FY 2015, OCP provided clarification and support for 71 separate postmarket matters. OCP issued draft guidance and continued to chair two FDA working groups, to address how current good

[1] These requests are now referred to as "pre-RFDs" or pre-requests for designation.
[2] FY 2014 numbers were changed to reflect updates to data presented in the FY 2014 OCP Performance Report. The updated data for FY 2014 is located in Appendix A.

manufacturing practices (CGMPs) apply to combination products. OCP also continued to work with the medical product Centers to resolve postmarket safety issues, registration and listing issues, and other postmarket regulatory 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 and scientific issues that arise regarding combination products. During FY 2015, OCP substantively reviewed the inter-Center consult process and information technology support system to identify potential enhancements for the inter-Center review process for combination products.

OCP documented 847 activities in FY 2015.[3] The topics of these activities included jurisdiction/classification, premarket review, and postmarket regulation.

[3] 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).

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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

On October 26, 2002, Congress enacted Medical Device User Fee and Modernization Act (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 the Office of Combination Products (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.

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.

Some 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 – 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. 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 request for designations (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 2015 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 2015 and updates FY 2014 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, 2015.

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) (see 21 CFR 3.4(b)) within 60 days of filing a RFD. OCP provides these required responses to formal RFDs that have a 60-day regulatory clock. OCP also provides responses to informal requests.[4]

Requirement Workload Trends: FY 2010 to FY 2015

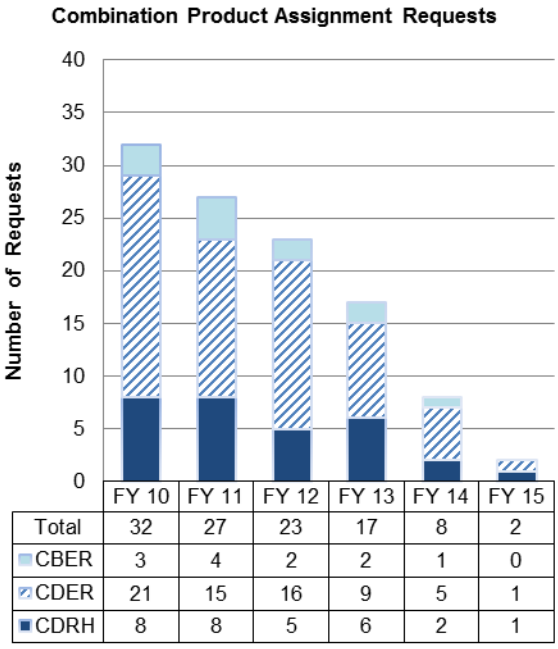
Classification and assignment workloads in FY 2015 are compared to the previous 5-year averages for the total number of combination product assignment requests and the total number of non-combination product classifications and assignment requests in the table below. Review workloads for both types of assignments are down compared to their respective 5 year averages. Specifically, the total formal combination product classifications and assignments are down 90 percent in FY 2015 and non-combination classifications and assignments are also down 36 percent for FY 2015.

OCP Requirement Workloads

Submission/Request	FY 10	FY 11	FY 12	FY 13	FY 14	FY 15	FY 10 to FY 14 5-Year Average	FY 15 Compared to 5-Year Average
Total Formal Combination Product Classifications/ Assignments	32	27	23	17	8	2	21	- 90%
Total Formal Non-Combination Product Classifications/ Assignments	12	12	10	14	9	7	11	- 36%

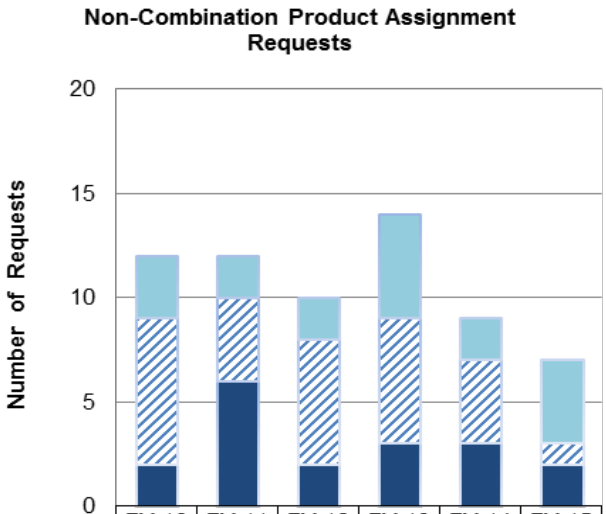
[4] Responses to informal requests for product classification and jurisdictional assignments do not have a required timeframe as formal RFDs. However, OCP attempts to respond to informal requests in a timeframe similar to formal RFDs (i.e., within 60 days). Information about informal requests (including the timeliness of OCP responses to informal inquiries) is provided on page 7.

The total number of formal combination product classifications and assignments issued continued to decrease in FY 2015 to the lowest number in the past 5 years.[5]



	FY 10	FY 11	FY 12	FY 13	FY 14	FY 15
Total	32	27	23	17	8	2
CBER	3	4	2	2	1	0
CDER	21	15	16	9	5	1
CDRH	8	8	5	6	2	1

The total number of formal product classifications and assignments for non-combination products decreased in FY 2015 to the lowest number in the past 5 years.



	FY 10	FY 11	FY 12	FY 13	FY 14	FY 15
Total	12	12	10	14	9	7
CBER	3	2	2	5	2	4
CDER	7	4	6	6	4	1
CDRH	2	6	2	3	3	2

[5] The decrease in formal RFD decisions has been accompanied by an increase in the number of informal inquires to OCP. See the section below titled OCP Informal Requests for Classification and Assignment.

RFD workload is based on 83 RFD submissions that were received during FY 2015. Of these 83 RFD submissions under consideration during FY 2015, decisions were issued for 9 submissions (11 percent), 69 RFD submissions were found by OCP to have insufficient information for filing (83 percent), [6] and 4 submissions were withdrawn by the sponsor prior to issuance of a formal decision (5 percent).[7] One RFD was pending at the end of FY 2015 undergoing a review of completeness, but had not been filed by September 30, 2015.

FY 2015 Review Performance

In FY 2015, 9 formal RFD assignment decisions were issued for combination (2) and non-combination (7) products, all within the 60-day review time statutory requirement (see tables on the following page). The combination product assignment times were 46 and 59 days, with a median product assignment time of 53 days. The non-combination product assignment times ranged from 38 to 60 days, with a median product assignment time of 54 days.

[6] OCP provided informal product classification and jurisdiction decisions for several of the RFDs that were submitted and not filed.
[7] Of the 4 withdrawn RFDs, 3 were withdrawn prior to filing and 1 was withdrawn after submission filing.

Workload for Number of Combination Product Assignments Issued

Determination	Product Assignments Issued*	Percent On Time*
Drug-Device	1	100%
Drug-Biologic	1	100%
Device-Biologic	0	NA
Drug-Device-Biologic	0	NA
Total	**2**	**100%**

* Does not include request for reconsideration responses, which are issued within the 15-day time frame provided by 21 CFR § 3.8. No requests for reconsiderations were submitted for combination products in FY 2015.

Workload for Number of Non-Combination Product Assignments Issued

Determination	Product Assignments Issued*	Percent On Time*
Drug	0	NA
Biologic	5	100%
Device	2	100%
Total	**7**	**100%**

* Does not include request for reconsideration responses, which are issued within the 15-day time frame provided by 21 CFR § 3.8. One request for reconsideration was submitted for a non-combination product in FY 2015.

OCP Informal Requests for Classification and Assignment:[8]

In addition to formal RFDs, OCP also provided decisions for informal requests for product classification and jurisdictional assignment (informal assessments)[9] in FY 2015. In the table below, OCP informal assessment review workloads in FY 2015 are compared to the previous 2-year averages.[10] Total informal assessments increased by 85 percent in FY 2015 compared to the 2-year average.

OCP Informal Assessment Workload

Informal Assessments	FY 13	FY 14	FY 15	FY 13 to FY 14 2-Year Average	FY 15 Compared to 2-Year Average
Total Informal Assessment Decisions	37	113	139	75	+85%

[8] See footnote 1: Effective 2016 these requests are referred to as "pre-RFDs."

[9] A sponsor may obtain a legally non-binding determination, of a product's classification and Center assignment by the submission of an informal inquiry to OCP. OCP's informal assessment enables the Agency (similar to a formal RFD determination) to assign a particular product to the appropriate agency component for premarket review and regulation (CDER, CBER, or CDRH).

[10] Data represents informal assessments for which a decision was issued during the respective fiscal year. Requests that were received but are still undergoing review or for which additional information was requested from the sponsor have not been included. More information regarding informal inquiries to OCP for which a decision has not been issued is included on page 21.

OCP responds to nearly all informal product classification and jurisdictional inquiries in a timeframe consistent with that mandated for formal RFDs (i.e. 60 days).[11] The table below shows the median and average review times for all informal product classification and jurisdictional assessments issued within the fiscal years shown. The time needed to review informal assessments increased in FY 2015 as compared to the previous 2 years. In FY 2015, the average number of review days was 24 and 95 percent of informal assessments decisions were answered in 60 days or less in FY2015.

OCP Informal Assessment Timeliness

Informal Assessment Timeliness Measures	FY 13	FY 14	FY 15
Median Review Days of Issued Informal Assessment Decisions	10	7	20
Average Review Days of Issued Informal Assessment Decisions	21	18	24
Percent of Informal Assessment Decisions Issued in 60 days	92%	94%	95%

[11] A few informal assessments each year may have review times that exceed 60 days.

OCP Requirements and Accomplishments

Type of Activity	FY 2015 Accomplishments
Issuing required RFD assignments within 60 days	OCP issued all required RFD assignments within 60 days. If OCP does not provide a written response within sixty days, the sponsor's recommendation respecting the classification and assignment of the product is considered to be the final determination.
Responding to 475 stakeholder informal inquiries[12]	OCP responded to 475 informal stakeholder inquiries related to product classification and jurisdiction assignment, primarily by e-mail. This represents a 92 percent increase in informal inquiries for classification and jurisdictional assignment compared to FY 2014.
Clarifying standards for product classification and preparing guidance on this issue	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 continued to participate in an FDA working group developing guidance to clarify classification standards for human tissue products.
Enhancing the timeliness, consistency, and clarity of jurisdictional decisions across FDA	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 and to facilitate identification of products that may raise jurisdictional or inspectional questions.

[12] The number of inquiries includes 139 requests for informal assessments reported above for which FDA provided feedback. An additional 336 inquires includes more general or procedural questions relating to product classification and assignment as well as queries about the classification or assignment of a particular product that did not provide sufficient information for the agency to provide feedback.

Timely and Effective Premarket Review

OCP is responsible for ensuring the timely and effective premarket review of combination products, including 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.

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 2015 by CBER, CDER, and CDRH included submissions filed or received in FY 2015. 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 2010 to FY 2015

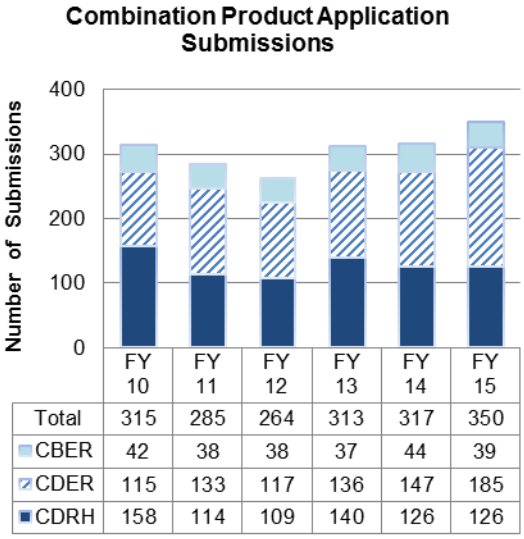
Review workloads in FY 2015 are compared to the previous 5-year averages for the total combination products submitted for review and the total inter-Center consult requests in the table below.

OCP Requirement Workloads

Submission/Request	FY 10	FY 11	FY 12	FY 13	FY 14*	FY 15	FY 10 to FY 14 5-Year Average	FY 15 Compared to 5-Year Average
Total Combination Products Submitted for Review by Centers	315	285	264	313	317	350	299	+ 17%
Total Inter-Center Consult Requests	466	530	660	828	1,013	932	699	+ 33%

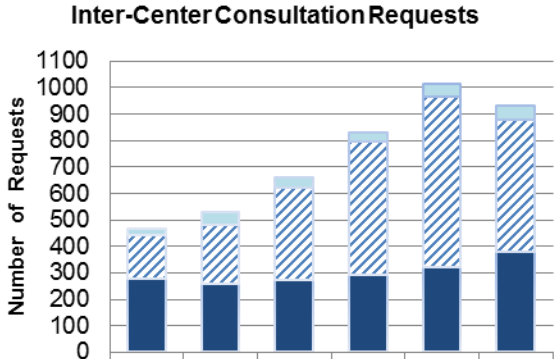
* FY 2014 numbers were changed to reflect updates to data presented in the FY 2014 OCP Performance Report.

The total number of combination products submitted for review increased in FY 2015. Fifty-three percent of the combination product application submissions received and categorized were led by CDER, followed by CDRH (36 percent) and CBER (11 percent).



	FY 10	FY 11	FY 12	FY 13	FY 14	FY 15
Total	315	285	264	313	317	350
CBER	42	38	38	37	44	39
CDER	115	133	117	136	147	185
CDRH	158	114	109	140	126	126

In FY 2015, the total number of inter-Center consult requests decreased for the first time in 6 years in FY 2015. The number of inter-Center consults decreased by 8% compared to the number of inter-Center consult requested in FY 2014, but was still higher than in all other years since FY 2010.



	FY 10	FY 11	FY 12	FY 13	FY 14	FY 15
Total	466	530	660	828	1013	932
CBER	25	51	40	31	48	53
CDER	162	220	350	506	643	499
CDRH	279	259	270	291	322	380

The table below reflects the number of product review forms during FY 2015, broken down by primary assigned Center and which Center requested the consult.[13]

Number of Premarket Reviews of Combination Products by Requesting and Assigned Center

Primary Assigned Center	CBER Lead	CDER Lead	CDRH Lead	Number of Consults
CBER	--	19	34	53
CDER	10	--	489	499
CDRH	8	372	--	380
Total	**18**	**391**	**523**	**932**

[13] 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 2015, as reported in the previous section.

The table below reflects the 350 original applications for initially classified into one of nine categories of combination products received in FY 2015. The same table reflecting applications received in FY 2014 is updated in Appendix A to reflect corrections and actions as of September 30, 2015. The majority of the applications (55 percent) were Original INDs, followed by Original 510(k)s (20 percent) and Original IDEs (13 percent). The most common combination product category was a device coated/impregnated/otherwise combined with a drug (26 percent), followed by a pre-filled drug delivery device/system (19 percent).

Workload by Combination Product Category Number

Application Type	1	2	3	4	5	6	7	8	9	Totals
Original NDAs	6	13	0	1	0	0	1	0	0	**21**
Original BLAs	0	0	7	0	0	0	0	0	0	**7**
Original PMAs	0	0	0	7	0	0	3	0	0	**10**
Original 510(k)s	6	0	0	54	0	0	4	3	3	**70**
Original INDs	11	52	20	5	5	39	2	54	5	**193**
Original IDEs	2	0	0	24	2	0	11	5	3	**47**
Original HDEs	0	0	0	0	0	0	2	0	0	**2**
Totals	**25**	**65**	**27**	**91**	**7**	**39**	**23**	**62**	**11**	**350**

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

Timeliness in Days of the Reviews of Combination Products

FDA is required to report the timeliness in review time for 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.

For PDUFA V performance goals, refer to

www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf.

Performance Goals for Original Applications†

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)

† 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 2014 combination product submissions and presents FDA's review performance on the FY 2015 combination product submissions through September 30, 2015.

FY 2014 and FY 2015 Review Performance

Final FY 2014 review goal performance is presented in the table below and were similar between FY 2014 and FY 2015.

Original Application Type	Review Type	Review Within	Number of Combination Products*	Median or Actual Review Time (Days)	Range of Review Time (Days)
NDAs	Priority	6 months	2	170	104 to 236
NDAs	Standard	10 months	16*	305	298 to 396
BLAs	Priority	6 months	1*	183	183
BLAs	Standard	10 months	8*	453	365 to 456
Expedited and Original PMAs	FDA Decision	180 or 320 days†	4*	180	87 to 318

Original Application Type	Review Type	Review Within	Number of Combination Products*	Median or Actual Review Time (Days)	Range of Review Time (Days)
510(k)s	SE or NSE decision	90 days	73*	81	17 to 147

* FY 2014 numbers were changed to reflect updates to data presented in the FY 2014 OCP Performance Report.

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

Preliminary FY 2015 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)
NDAs	Priority	6 months	5	180	121 to 334
NDAs	Standard	10 months	16	304	302 to 365
BLAs	Priority	6 months	1	242	242
BLAs	Standard	10 months	6*	0	0
Expedited and Original PMAs	FDA Decision	180 or 320 days†	10	175	170 to 180
510(k)s	SE or NSE decision	90 days	69	84	13 to 110

* 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.

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

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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 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 2015 accomplishments related to premarket review are included in the table below.

Type of Activity	FY 2015 Accomplishments
Developing guidance and regulations	• In 2015, OCP issued with the medical product Centers and ORA a draft guidance for industry on CGMPs for combination products. • OCP chaired a working group to prepare the final guidance on CGMP 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 also co-chaired a committee on combination products of the Association for the Advancement of Medical Instrumentation (AAMI) that prepared TIR (Technical Information Report) 48 on CGMPs for combination products, published by AAMI in 2015, targeted to combination products manufacturers to help outline best practices with respect to CGMP obligations. • OCP chaired a cross-center working group to enhance the inter-Center review process and practices. • OCP also chaired a cross center working group to develop a guidance document to clarify the role of human factors studies for combination products.
Responding to 700 requests for assistance from Centers and sponsors relating to premarket review issues[14]	OCP received 700 requests for assistance, the responses to which 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, photodynamic therapy, wound healing products, generic drugs that include devices, product-specific alignment of drug and device labeling, and development considerations for electronic cigarettes and mobile communication technologies.

[14] 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 2015 Accomplishments
Developing possible regulatory pathways for new products intended to be used with another sponsor's already-approved product	OCP continued to work with the Centers and OCC to assess approaches for resolving the complex legal and public health issues associated with the marketing of products intended for use with other legally marketed products, including assessing the appropriateness of different marketing authorization pathways, labeling, and coordination with and between product sponsors.
Participation in other inter-Center and agency-wide working groups to clarify issues related to combination products	OCP 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, combination product drug shortage concerns, package type terms, and flow restrictors. OCP also participated in agency-wide working groups such as FDA's Task Force on Antimicrobial Resistance. OCP participated in the CDER development of guidance for "Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use" available at: www.gpo.gov/fdsys/pkg/FR-2015-10-22/html/2015-26849.htm OCP provided assistance to the CDER electronic submission working group to achieve guidance document clarity on where to submit device constituent part information when using the CDER/CBER ECTD format.
Serving as a resource for FDA staff on the appropriate use and interpretation of the combination product categorization algorithm and associated categories	All premarket applications in CBER, CDER, and CDRH are to be categorized as to whether they concern a combination product, and if so, what type.

Practice of the Inter-Center 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. OCP responded to external industry requests to host cross-center early development meetings on bundled issues to minimize redundant product meetings.

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 2015.

Type of Activity	FY 2015 Accomplishments
Consultative/Collaborative Review Process	• Actively tracking, monitoring, and following up on a total of 932 inter-Center consult requests on combination products under review to ensure the requesting Center received timely feedback.
Providing Significant Facilitation or Assistance	• Novel drug-device cancer therapies • Injector delivery systems (including intrathecal systems) • Traditional products with novel combination uses • Medical imaging drugs and devices • Coordination of premarket CGMP inspections • Import-export of combination products or their constituent parts • Inter-Center compliance and safety evaluator processes for premarket evaluation and postmarket safety matters • Registration and listing and associated information technology considerations • Regulatory considerations for a monograph drug for use with a device constituent part or for a Class I device for use with a drug • Risk determination and need for investigational application assessments • Unique device identifiers and standardized numerical identification • Application of IND and IDE requirements for combination products • Application of user and facility fees to combination products • CDRH development of guidance on premarket regulation of drug-eluting stents • OCP also continues to chair the inter-Center working group to develop solutions for ensuring labeling consistency between imaging drugs and imaging devices
Consultative/Collaborative Review Process and Procedures Development	• OCP chairs a working group on classification and consultation for container/closures that also deliver drugs/biologics. • OCP chairs an inter-Center working group to revise and enhance the inter-Center consult process standard operating procedures including IT enhancements.

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. 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 2015 accomplishments related to the consistency and appropriateness of postmarket regulation are included in the table below.

Type of Activity	FY 2015 Accomplishments
Providing clarification and support on separate postmarket matters to ensure consistent and appropriate postmarket regulation of combination products	OCP addressed 71 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.
Developing regulations	In FY 2015, OCP continue to work with OCC and the Centers on clearance of a final rule on postmarketing safety requirements for combination products, and with Centers to update information technology systems to support tracking, sharing and assessment of safety reports for combination products.
Guidance development	OCP continued to chair 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).
Procedures development	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

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.

In addition to disputes related to timeliness, OCP may also receive requests for dispute resolution and/or mediation for other review issues (e.g., inter-office review dispute resolution or requests by product sponsors for assistance in understanding a review division's intent regarding issued decisions).

Timeliness in Days of Dispute Resolutions Regarding Combination Products

FDA is to report the timeliness in days of dispute resolutions regarding combination products. For the 12th consecutive year, no formal requests to resolve a dispute regarding the timeliness of a combination product review were received during FY 2015. 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 officially documented activities performed during FY 2015. These are summarized in the table below. These are summarized in the table below. The Jurisdiction/Classification Assignments and Issues increased by 81 percent in FY 2015 compared to the 5-year average.

Number of OCP Documented Activities*

OCP Activities	FY 10	FY 11	FY 12	FY 13	FY 14	FY 15	FY 10 to FY 14 5-Year Average	FY 15 Compared to 5-Year Average
Total Activities by Stakeholder[15]	641	682	756	603	760	847	688	+ 23%
Total Activities by Issue Type[16]								
Jurisdiction/Classification Assignments and Issues[17,18]	303	265	268	233	248	475	263	+ 81%
Premarket Review Issues	551	495	388	390	650	700	495	+ 41%
Postmarket Regulation Issues	60	57	33	57	110	71	63	+ 13%

* 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 2015 OCP accomplishments with regard to two categories of efforts: external outreach and regulatory initiatives.

External Outreach

[15] Total Activities by Stakeholder represents the sum of the Premarket Review Issues and Postmarket Regulation Issues categories. The activities reported do not include formal OCP activities (e.g., responses to RFD submissions).
[16] Activities may be reported for multiple subcategories.
[17] The Jurisdiction/Classification Assignments category listed in the table is a subset of the larger Premarket Review Issues category.
[18] The Jurisdiction/Classification Assignments category include all inquiries to OCP for the respective fiscal year that pertain to product classification and jurisdiction issues. As such, inquiries are included regardless of whether a product classification and jurisdictional decision was issued (e.g., pending decisions, inquiries for which additional information was requested, consultations regarding whether a jurisdictional assessment would be needed that are requested by the FDA Centers). The 139 inquiries for FY 2015 (reported elsewhere in this report) that resulted in informal product classification and jurisdictional assessment decisions are included in the total number of issues provided.

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 diagnostics, injector clinical development options, standards, and future industry needs. Examples of FY 2015 outreach activities are included in the tables on the following pages.

Type of Activity	FY 2015 Accomplishments
Presentations and outreach activities	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: • Regulatory Affairs Professionals Society conference • BIOMEDevice Conference • FDA/Xavier University MedCon Medical Device Conference • Association for the Advancement of Medical Instrumentation/FDA International Conference on Medical Device Standards and Regulation • Drug Information Association Third Annual Conference on Combination Products • Parenteral Drug Association/FDA Joint Regulatory Conference • Medical Device Manufacturers Association • Informa Annual Conference on Combination Products • Drug Information Association Annual Meeting • Medical Device Summit: Combination Products

Regulatory Initiatives

OCP activities include efforts to assist in advancing initiatives important to and affecting the regulation of combination products. Examples of regulatory activities pursued in FY 2015 are included in the following table.

Type of Activity	FY 2015 Accomplishments
Continuing to contribute to the advancement of innovative products initiatives	• OCP assisted in determining the appropriate regulatory pathway for novel technology diagnostics and biomarkers under review for use with drug or biological products. • OCP continued to participate in the Intra-agency FDA Task Force on Nanotechnology and other nanotechnology-related activities. • 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, unique identifiers for devices and combination products that include them, and regulation of biosimilar biological products. • OCP coordinated development of consistent trial designs for certain novel cancer chemotherapeutic dedicated delivery systems. • OCP provided internal feedback on ISO standards development for certain syringes. • OCP provided input into the 21st Century Cures and other innovative legislative initiatives relating to the regulation of combination products.
Continuing to actively participate in the FDA Enterprise Initiatives and the development of requirements on drug and device registration and listing	OCP continued to serve as liaison to several FDA-wide electronic database initiatives with the goal of enhancing the infrastructure necessary to ensure the safety and effectiveness of combination products and development of FDA-wide medical product databases applicable to combination products.

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Appendix A: FY 2014 Updated Performance Detail

The table below reflects the 317 original applications initially classified into one of nine categories of combination products received in FY 2014.

Workload by Combination Product Category Number

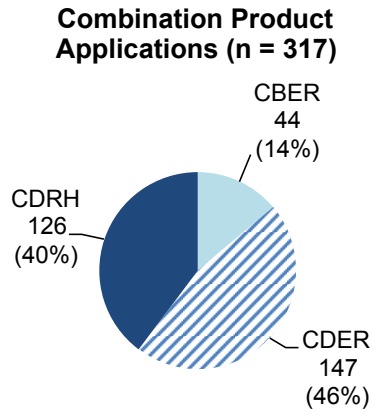
Application Type	1	2	3	4	5	6	7	8	9	Totals
Original NDAs	3	14	0	0	0	0	0	0	1	**18**
Original BLAs	0	0	4	0	0	0	0	0	5	**9**
Original PMAs	0	0	0	2	1	0	1	0	1	**5**
Original 510(k)s	5	0	0	41	4	0	6	10	16	**82**
Original INDs	15	47	20	11	1	27	2	26	4	**153**
Original IDEs	0	0	0	20	3	0	20	4	3	**50**
Original HDEs	0	0	0	0	0	0	0	0	0	**0**
Totals	**23**	**61**	**24**	**74**	**9**	**27**	**29**	**40**	**30**	**317**

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 2014 by Center lead, as of September 30, 2015.



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:

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the OCP Home Page at: www.fda.gov/CombinationProducts/default.htm.