FY 2016

PERFORMANCE REPORT TO CONGRESS

for the

Office of Combination Products

as required by the

Medical Device User Fee and Modernization Act of 2002

Commissioner's Report

I am pleased to submit the Food and Drug Administration's (FDA or the Agency) fiscal year (FY) 2016 annual report to Congress for the Office of Combination Products (OCP). This report includes data from the thirteenth full year since OCP was established, as mandated by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA), P.L. 107-250, 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 constituent parts that would normally be regulated under different types of regulatory authorities, and frequently by different FDA medical product Centers, which raises 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.

Scott Gottlieb, M.D.
Commissioner of Food and Drugs

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Executive Summary

FDA established OCP on December 24, 2002, as required by 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 medical product Centers, the timely and effective premarket review of such applications, and consistent and appropriate postmarket regulation of these products.

This document presents OCP's annual report to Congress and covers activities and accomplishments during FY 2016 (October 1, 2015, through September 30, 2016). OCP's activities and performance for FY 2016 that are highlighted in this report include:

- **Prompt Assignment of Combination Products**. In FY 2016, OCP continued to clarify the jurisdictional assignment of combination products and to provide prompt Request for Designation (RFD) decisions. OCP issued two combination-product and two non-combination-product RFD decisions, with every assignment meeting the 60-day statutory decision time requirement. OCP also provided timely classification and jurisdictional assessments for 157 separate pre-RFD submissions.[1] To enhance the RFD process, OCP—in collaboration with the Office of Medical Products and Tobacco (OMPT), CDER's Lean Management Staff, and the FDA medical product Centers—made changes to our internal procedures for responding to communications from sponsors regarding preliminary product classification assessments from OCP. The pre-RFD process is the result of such cooperative efforts.

- **Timely and Effective Premarket Review**. In FY 2016, OCP continued to make significant contributions to the premarket review of combination products by responding to 978 requests for assistance from Centers and sponsors. This is a 40 percent increase from the 700 requests received in FY 2015. OCP, in conjunction with the Centers, implemented major changes intended to improve the inter-Center consult process. The Lean Management mapping process was utilized to analyze the current state of the inter-Center consult processes for premarket reviews; identify potential causes of delays and inefficiency; and develop a revised process to enhance efficiency, coordination, and consistency of review of combination products. The revised process is in the pilot phase and is expected to be broadly implemented by the end of FY 2017. Other OCP activities relating to premarket review included chairing and/or participating in a number of inter-Center working groups to examine complex regulatory issues, clarifying regulatory standards, addressing challenging categories of products, identifying and resolving specific product issues, updating the premarket review process, and determining developmental considerations for combination products.

- **Combination Product Review**. FDA received 357 original premarket applications for combination products in FY 2016. This is a 5 percent increase from the 341[2] received in

[1] Informal requests for product classification and jurisdictional assessment/feedback are now referred to as "pre-RFDs" or pre-requests for designation.
[2] Refer to the appendix on page A-1 for the FY 2015 updated performance data.

FY 2015. Inter-Center consulting reviews for combination products increased to 1,130 for FY 2016 from 932 in FY 2015. Examples of approved combination products can be found on the OCP website: http://www.fda.gov/CombinationProducts/default.htm.

- **Consistent and Appropriate Postmarket Regulation**. In FY 2016, OCP provided clarification and support for 50 separate postmarket matters. OCP continued to chair two FDA working groups to address how current good manufacturing practices (CGMPs) apply to combination products, which included the finalization of guidance, and also led cross-cutting training of compliance and inspections staff. OCP also continued to work with FDA's medical product Centers to finalize the postmarket safety reporting rule for combination products. The group also helped to resolve postmarket safety issues, registration and listing issues, postmarket change submissions, and other postmarket regulatory issues pertaining to specific combination products.

- **Additional Activities and Accomplishments**. In addition, the Agency created a cross-cutting decisional Combination Products Policy Council consisting of senior leaders, including from the FDA medical product Centers and OCP. The Council was chartered to discuss, resolve, and ensure implementation of solutions to complex policy questions for combination products. Moreover, 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.

OCP documented 1,028 activities in FY 2016.[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 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 website at http://www.fda.gov/CombinationProducts/default.htm.

Description of Combination Products

Combination products are developed to enhance the safety and effectiveness of the component 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 combination products, including 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 FDA 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 (FD&C Act) required 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 and overseeing progress of, 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, drug, or combination product, as well as requests for product assignment.

Performance Presented in This Report

This section includes FY 2016 OCP activities and accomplishments in the assignment of combination products and in coordinating the premarket review and postmarket regulation of combination products. OCP is also required to provide an annual performance assessment for the various combination product applications. Accordingly, this section also provides performance information for FY 2016 and updates FY 2015 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, 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, 2016.

Prompt Assignment of Combination Products

OCP is required to assign primary jurisdiction for combination products (i.e., Center assignment) based on the product's primary mode of action (PMOA) (see 21 CFR 3.4(b)) in response to RFDs. RFD submissions are subject to a statutory 60-day deadline. OCP also provides assessments concerning product classification Center and assignment in response to pre-RFDs.[4]

Requirement Workload Trends: FY 2011 to FY 2016

Classification and assignment workloads in FY 2016 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 87 percent in FY 2016 and non-combination classifications and assignments are also down 80 percent for FY 2016.

OCP Requirement Workloads[5]

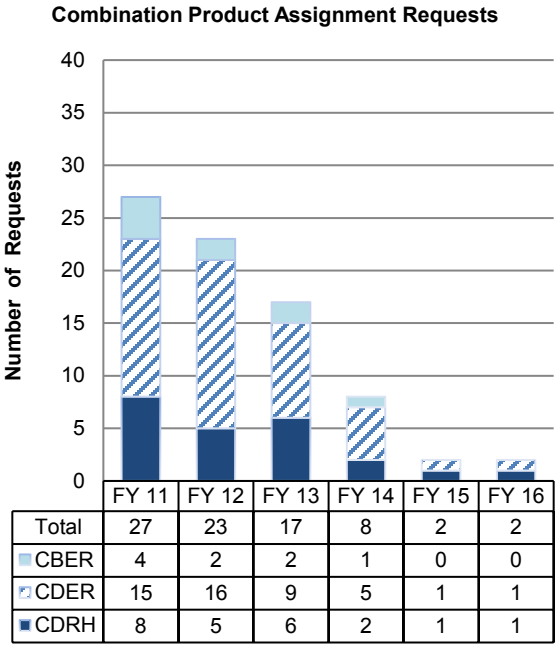
RFD Submissions	FY 11	FY 12	FY 13	FY 14	FY 15	FY 16	FY 11 to FY 15 5-Year Average	FY 16 Compared to 5-Year Average
Total Formal Combination Product Classifications/ Assignments	27	23	17	8	2	2	15	- 87%
Total Formal Non-Combination Product Classifications/ Assignments	12	10	14	9	7	2	10	- 80%

[4] Responses pre-RFDs requesting assessments concerning product classification and Center assignment do not have a required timeframe. However, OCP attempts to respond to pre-RFDs in a timeframe similar to RFDs (i.e., within 60 days). Information about pre-RFDs (including the timeliness of OCP responses to informal inquiries) is provided on page 7.

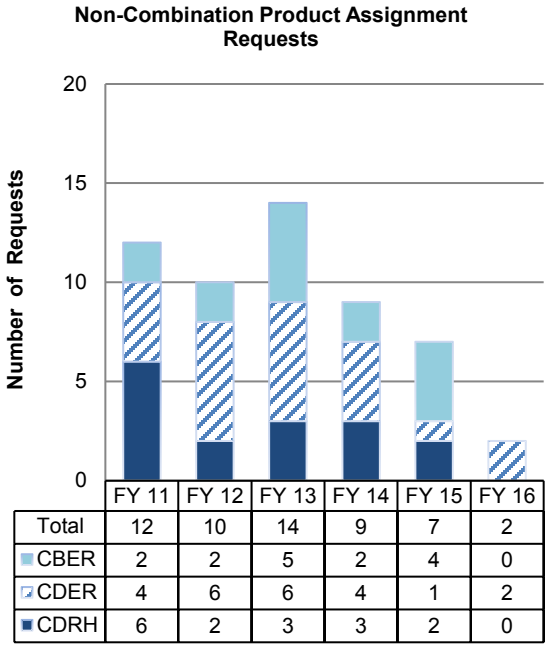
[5] The decrease in RFD decisions has been accompanied by an increase in the number of pre-RFD assessments provided by OCP. See the section below titled "OCP Pre-RFD Requests for Classification and Assignment."

The total number of RFD combination product classifications and assignments issued in FY 2016 were the same as in FY 2015 and continued to be the lowest number in the past 6 years.

The total number of formal product classifications and assignments for non-combination products decreased in FY 2016 to the lowest number in the past 6 years.



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



	FY 11	FY 12	FY 13	FY 14	FY 15	FY 16
Total	12	10	14	9	7	2
CBER	2	2	5	2	4	0
CDER	4	6	6	4	1	2
CDRH	6	2	3	3	2	0

RFD workload is based on 58 RFD submissions that were received during FY 2016. Of these 58 RFD submissions under consideration during FY 2016, decisions were issued for 4 submissions (7 percent), 49 RFD submissions were found by OCP to have insufficient information for filing (84 percent), and 2 submissions were withdrawn by the sponsor prior to issuance of a formal decision (3 percent).[6] One filed RFD was undergoing review at the end of FY 2016, but a decision had not been issued. Furthermore, two RFDs were undergoing a review of completeness, but had not been filed by September 30, 2016.

FY 2016 Review Performance

In FY 2016, four RFD assignment decisions were issued for combination (two) and non-combination (two) products, all by the statutorily mandated 60-day deadline (see tables on the following page). The combination product assignment times were 45 and 47 days, with a median product assignment time of 46 days. The non-combination product assignment times were both 60 days.

Workload and Performance for Number of Combination Product Assignments Issued

Determination	Product Assignments Issued*	Percent on Time*
Drug-Device	2	100%
Drug-Biologic	0	NA
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. One request for reconsideration was submitted for a combination product in FY 2016.

Workload and Performance for Number of Non-Combination Product Assignments Issued

Determination	Product Assignments Issued*	Percent on Time*
Drug	2	100%
Biologic	0	NA
Device	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 reconsideration were submitted for a non-combination product in FY 2016.

Pre-RFD Submissions to OCP Requesting Classification and Center Assignment Assessments[7]

In addition to RFDs, OCP also provided preliminary feedback/assessments for pre-RFD submissions for product classification and Center assignment[8] in FY 2016. The pre-RFD

[6] Both of the RFDs were withdrawn prior to filing.
[7] See footnote 1. Effective FY 2016, these requests are referred to as "pre-RFDs." Due to this change, the data shown for FY 2013 through FY 2015 are now referred to as "pre-RFD" data and includes both internal and external requests. These requests were presented as "informal assessments" in prior OCP performance reports.
[8] A sponsor may obtain preliminary feedback on a product's classification and/or Center assignment, or on what information to provide in an RFD, by submitting a pre-RFD to OCP.

process may be preferable to the more formal RFD process when a sponsor would like to engage FDA using a more interactive approach, a course that may be especially helpful when a medical product is at an early stage in its development or when a sponsor is contemplating whether to develop a specific product (or what configuration of that product to pursue). In the table below, OCP pre-RFD submission review workloads in FY 2016 are compared to the previous 3-year averages.[9] Total pre-RFD submissions increased by 64 percent in FY 2016 compared to the 3-year average.

OCP Pre-RFD Submission Workload

Pre-RFD Assessments	FY 13	FY 14	FY 15	FY 16	FY 13 to FY 15 3-Year Average	FY 16 Compared to 3-Year Average
Total Pre-RFD Assessments	37	113	139	157	96	+64%

[9] Data represent pre-RFDs to which OCP received complete information and responded with feedback on product classification or Center assignment during the respective fiscal year. Pre-RFD submissions were not included in this data if they were still undergoing review or the requests contained incomplete information.

OCP responded to nearly all pre-RFD submissions in a timeframe consistent with that mandated for formal RFDs (i.e., 60 days). The table below shows the median and average review times for all pre-RFD classification and Center assignment assessments issued within the fiscal years shown. The average time to review pre-RFD submissions increased in FY 2016 as compared to the previous 3 years. In FY 2016, the average number of review days was 30, and 96 percent of informal assessments decisions were answered in 60 days or less.

Pre-RFD Submission Timeliness

Pre-RFD Assessment Timeliness Measures	FY 13	FY 14	FY 15	FY 16
Median Review Days	10	7	20	21
Average Review Days	21	18	24	30
Percent of Assessments Issued in 60 days	92%	94%	95%	96%

OCP Requirements and Accomplishments

Type of Activity	FY 2016 Accomplishments
Issuing required RFD assignments within 60 days	OCP issued all RFD assignments by the statutory 60-day deadline.
Responding to informal stakeholder inquiries including, pre-RFDs	OCP responded to 712 stakeholder inquiries related to product classification and Center assignment. These 712 inquiries include 157 pre-RFDs and an additional 555 inquiries of more general or procedural questions relating to product classification and assignment, as well as queries about the classification or assignment of a particular product where the sponsor did not provide sufficient information for the Agency to provide feedback. This represents a 50 percent increase in informal inquiries for classification and Center assignment compared to FY 2015.
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 participated in a Part 15 panel and continued to participate in an FDA working group on 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 product classification and jurisdictional meetings with CBER, CDER, CDRH, and OCC staff to exchange information and discuss challenging product classification and Center assignment issues before the FDA. OCP continued to provide training to review staff, including personnel from CBER, CDER, and CDRH, as well as Office of Regulatory Affairs inspectors, on product classification and Center assignment.

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 website at http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm135860.htm.[10]

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 2016 by CBER, CDER, and CDRH included submissions filed or received in FY 2016. The number of combination product submissions is a small subset of the total number of medical product 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 are 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 are 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 304 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 is based on FDA first cycle review performance for PDUFA V goals. For MDUFA III goals, median review times are based on total MDUFA III decision review time. Actual review time is used when only one action was measured.

[10] On December 13, 2016, during FDA's 2017 fiscal year, the 21st Century Cures Act was signed into law. Section 3038 of this legislation amended section 503(g) of the FD&C Act (21 USC 353(g)), the principal provision of the FD&C Act with respect to combination products. The amendments to section 503(g) included some additions to the congressional reporting requirements for OCP. Among other changes, consistent with these additional reporting requirements, the FDA FY 2017 report will include, for combination products, data on timely and effective premarket review of abbreviated new drug applications (see FD&C Act section 505(j) (21 USC 355(j)) and de novo classifications (see FD&C Act section 315(f) (21 USC 360c(f)).

Requirement Workload Trends: FY 2011 to FY 2016

Review workloads in FY 2016 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.

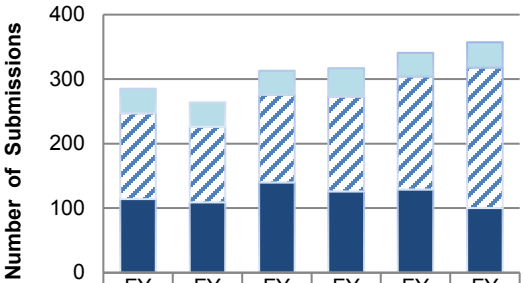
OCP Requirement Workloads

Submission/Request	FY 11	FY 12	FY 13	FY 14	FY 15*	FY 16	FY 11 to FY 15 5-Year Average	FY 16 Compared to 5-Year Average
Total Combination Products Submitted for Review by Centers	285	264	313	317	341	357	304	+ 17%
Total Inter-Center Consult Requests	530	660	828	1,013	932	1,130	776	+ 42%

* FY 2015 numbers were changed to reflect updates to data presented in the FY 2015 OCP performance report.

The total number of combination products submitted for review increased in FY 2016. Of the combination product application submissions received and categorized, 61 percent were led by CDER, followed by CDRH (28 percent) and CBER (11 percent).

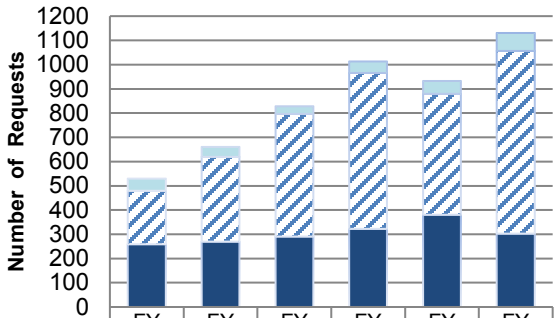
Combination Product Application Submissions



	FY 11	FY 12	FY 13	FY 14	FY 15	FY 16
Total	285	264	313	317	341	357
CBER	38	38	37	44	37	39
CDER	133	117	136	147	175	218
CDRH	114	109	140	126	129	100

The total number of inter-Center consult requests increased in FY 2016 to the highest number in the past 6 years. The number of inter-Center consults increased by 42 percent as compared to the previous 5-year average.

Inter-Center Consultation Requests



	FY 11	FY 12	FY 13	FY 14	FY 15	FY 16
Total	530	660	828	1013	932	1130
CBER	51	40	31	48	53	74
CDER	220	350	506	643	499	754
CDRH	259	270	291	322	380	302

The table below reflects the number of Inter-Center consult request forms used during FY 2016, broken down by primary assigned Center and which Center requested the consult.[11]

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

Primary Assigned Center	CBER Consulted	CDER Consulted	CDRH Consulted	Number of Consults
CBER	--	7	2	9
CDER	28	--	300	328
CDRH	46	747	--	793
Total	**74**	**754**	**302**	**1,130**

[11] 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 2016, as reported in the previous section.

The table below reflects the 357 original applications for combination products received in FY 2016 under the identified seven application types, and presents their initial classification into one of nine categories.[12] The same table reflecting applications received in FY 2015 is updated in Appendix A to reflect corrections and actions as of September 30, 2016. The majority of the applications (62 percent) were original INDs, followed by original 510(k)s (21 percent) and original IDEs (8 percent). The most common combination product category was *possible combination based on mutually conforming labeling of separate products* (25 percent), followed by *device coated/impregnated/otherwise combined with drug* (21 percent).

Workload by Combination Product Category Number

Application Type	1	2	3	4	5	6	7	8	9	Totals
Original NDAs	5	13	0	0	0	0	0	0	1	**19**
Original BLAs	1	0	7	0	1	0	0	0	0	**9**
Original PMAs	0	0	0	3	1	0	0	0	0	**4**
Original 510(k)s	9	0	0	51	1	0	10	1	2	**74**
Original INDs	5	54	14	11	0	51	1	83	2	**221**
Original IDEs	2	0	0	11	4	0	2	6	5	**30**
Original HDEs	0	0	0	0	0	0	0	0	0	**0**
Totals	**22**	**67**	**21**	**76**	**7**	**51**	**13**	**90**	**10**	**357**

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

[12] The classifications are presented as "initial" because adjustments are made to these numbers for each fiscal year to reflect corrections and subsequent actions that may inform classification status, such as the ultimate status of products initially placed in category 8 (for certain possible combination products). An updated version of the same table for applications received in FY 2015 is provided in Appendix A to reflect corrections and actions as of September 30, 2016.

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: http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM295454.pdf.

For PDUFA V performance goals, refer to: http://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 of 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 2015 combination product submissions and presents FDA's review performance on the FY 2016 combination product submissions through September 30, 2016.

FY 2015 and FY 2016 Review Performance

Final FY 2015 review goal performance is presented in the table below and was similar between FY 2015 and FY 2016.

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	181	121 to 336
NDAs	Standard	10 months	16	305	301 to 397
BLAs	Priority	6 months	1	242	242
BLAs	Standard	10 months	3*	365	359 to 455
Expedited and Original PMAs	FDA Decision	180 or 320 days†	8*	339	171 to 380
510(k)s	SE or NSE Decision	90 days	75*	83	13 to 110

* FY 2015 numbers were changed to reflect updates to data presented in the FY 2015 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 2016 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	3	174	165 to 183
NDAs	Standard	10 months	16	304	303 to 304
BLAs	Priority	6 months	2*	0	0
BLAs	Standard	10 months	7	334	303 to 364
Expedited and Original PMAs	FDA Decision	180 or 320 days†	4*	177	177
510(k)s	SE or NSE Decision	90 days	74	86	9 to 101

* Included in this count are BLAs and 510(k)s 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.

OCP Requirements and Accomplishments

Premarket Review Process

OCP continued to facilitate the premarket review processes for combination products having complex regulatory issues. OCP fostered 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 provided 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 led or participated in meetings and discussions to ensure continued and consistent communication between sponsors and FDA review staff. OCP FY 2016 accomplishments related to premarket review are included in the table below.

Type of Activity	FY 2016 Accomplishments
Developing guidance and regulations	OCP chaired a cross-Center working group to develop a guidance document to clarify the role of human factors studies for combination products. In February 2016, OCP, along with the FDA medical product Centers, issued the draft guidance "Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development," available at. https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm484345.pdf (See also the discussion of CGMP-related guidance and training under the "Consistent and Appropriate Postmarket Regulation" section.)
Responding to requests for assistance from Centers and sponsors relating to premarket review issues[13]	OCP received 978 requests for assistance, the responses to which contributed to ensuring the timely and effective review of combination products. OCP addressed issues related to: novel drug and biological product delivery systems, photodynamic therapy, wound healing products, generic drugs that include devices, consistency and clarity of labeling, and developmental considerations for combination products with mobile communication technologies.
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 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. OCP also participated in Agency efforts to work with the imaging product industry on specific considerations relating to combined use of imaging devices with imaging agents.

[13] The number of premarket activities reported in this section includes the 712 stakeholder jurisdictional inquiries reported above. This is because, generally, product classification and jurisdictional determinations are requested and made in the premarket setting.

Type of Activity	FY 2016 Accomplishments
Participating 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 products and tissues, product labeling, wound care products, flow restrictors, metered dose inhalers and dry powder inhalers, guidance and citizen petition responses for specific types of generic combination products, guidance on comparative human factors studies for generic drug-led and interchangeable biologic-led combination products, and a final rule on the use of symbols in device and device-led combination product labeling. OCP also participated in Agency-wide working groups such as FDA's Task Force on Antimicrobial Resistance and a workgroup focused on classification of certain wound care products containing antimicrobials. 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: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm468228.pdf. OCP and CDRH participated in the CDER electronic submission working group to further clarify where to provide device constituent part information when using the CDER/CBER ECTD format. The revised September 2016 guidance document, "Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications," is available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf
Serving as a resource for FDA staff on the appropriate use and interpretation of combination product categorization for premarket submissions	OCP assisted staff in CBER, CDER, and CDRH in determining the correct combination product categories for data reporting purposes.

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 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.

Type of Activity	FY 2016 Accomplishments
Consultative/collaborative review process	• Actively tracked, monitored, and followed up on a total of 1,130 inter-Center consult requests on combination products under review to ensure the requesting Center received timely feedback.
Providing significant facilitation or assistance	Provided significant assistance with respect to the following categories of products and other premarket regulatory issues: • 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 21 CFR Part 4 to premarket submissions under review • CDRH development of guidance on premarket regulation of drug-eluting stents
Development of consultative/collaborative review process and procedures	• OCP chaired a working group on consultation for containers/closures that also deliver drugs/biologics. • OCP participated in an Agency working group, utilizing the Lean Management mapping process, to examine, revise, and enhance the inter-Center consult process. Additionally, significant improvements were made to the form used to manage consults between Centers. • OCP lead efforts to improve staff access to IT systems needed for the review of combination products. • OCP, along with the Office of the Commissioner and the FDA medical product Centers, initiated a pilot for adjustments to the inter-Center consult process intended to enable timely and consistent coordination to generate effective submission reviews.

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 2016 accomplishments related to the consistency and appropriateness of postmarket regulation are included in the table below.

Type of Activity	FY 2016 Accomplishments
Providing clarification and support on separate postmarket matters to ensure consistent and appropriate postmarket regulation of combination products	OCP addressed 50 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 2016, OCP continued to work with OCC and the Centers on clearance of a final rule on postmarketing safety requirements for combination products. OCP also worked with Centers to update information technology systems to support tracking, sharing, and assessment of safety reports for combination products.
Guidance development	• OCP chaired a working group to prepare final guidance on CGMP and to augment associated training materials for investigators and compliance staff. • OCP and Center experts presented training to FDA field and headquarters staff on CGMPs. The final guidance "Current Good Manufacturing Practice Requirements for Combination Products," along with enhanced training, is intended to facilitate timely, effective premarket review of combination products subject to premarket authorization by FDA. • OCP also continued to co-chair 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 2016, the report is targeted to combination products manufacturers to help outline best practices with respect to CGMP obligations. The committee also began work on a TIR on risk management for combination products. • OCP also continued to work with Centers on guidance for combination product registration and listing and on finalization of the draft guidance on postmarket change submissions for combination products.

Type of Activity	FY 2016 Accomplishments
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 thirteenth consecutive year, no formal requests to resolve a dispute regarding the timeliness of a combination product review were received during FY 2016. 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 2016. These are summarized in the table below.

Number of OCP Documented Activities*

OCP Activities	FY 11	FY 12	FY 13	FY 14	FY 15	FY 16	FY 11 to FY 15 5-Year Average	FY 16 Compared to 5-Year Average
Total Activities by Stakeholder[14]	682	756	603	760	847	1028	730	+ 41%
Total Activities by Issue Type								
Jurisdiction/Classification Assignments and Issues[15,16]	265	268	233	248	475	712	298	+ 139%
Premarket Review Issues	495	388	390	650	700	978	525	+ 86%
Postmarket Regulation Issues	57	33	57	110	71	50	66	- 24%

* 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 2016 OCP accomplishments with regard to two categories of efforts: external outreach and regulatory initiatives.

[14] "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).
[15] The "Jurisdiction/Classification Assignments and Issues" category listed in the table is a subset of the larger "Premarket Review Issues" category.
[16] The "Jurisdiction/Classification Assignments and Issues" 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, requests from FDA medical product Centers regarding whether a jurisdictional assessment would be needed). The 157 inquiries for FY 2016 (reported elsewhere in the Executive Summary) that resulted in informal product classification and jurisdictional assessment decisions are included in the total number of issues provided.

External Outreach

OCP conducts outreach activities to share information on FDA assignment and regulation of combination products by participating in industry conferences and meeting with trade associations and coalitions representing the drug, device, biological product, and combination product industries (e.g., Combination Products Coalition, Advanced Medical Technology Association, Association for Advancement of Medical Instrumentation). 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 2016 outreach activities are included in the tables on the following pages.

Type of Activity	FY 2016 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: • Association for the Advancement of Medical Instrumentation/FDA International Conference on Medical Device Standards and Regulation • Drug Information Association Fourth Annual Conference on Combination Products • Parenteral Drug Association/FDA Joint Regulatory Conference • Informa Annual Conference on Combination Products • Drug Information Association Annual Meeting • NIH Neuroscience Forum: Developing Multimodal Therapies for Brain Disorders • Ministry of Foreign Affairs of Denmark FDA Seminar on Combination Products • FDLI 2016 Annual Conference

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 2016 are included in the following table.

Type of Activity	FY 2016 Accomplishments
Continuing to contribute to the advancement of innovative product initiatives	• OCP participated in an assessment of the procedures for sponsors to obtain informal feedback on product classification and assignment, in support of the pre-RFD program. • OCP assisted in determining the appropriate regulatory pathway for novel technology diagnostics and biomarkers under review for use with drug or biological products. • 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 considerations for visualization of particulates in injectable solutions. • OCP provided assistance on combination product considerations for guidance and regulations developed by Centers. Topics included the development and premarket review of companion diagnostics and other products intended for use with other products, unique identifiers for devices and combination products that include them, regulation of biosimilar biological products, generic developmental issues, and expanding non-prescription access to drugs. • OCP coordinated development of consistent trial designs for certain novel delivery systems dedicated to cancer chemotherapeutics. • OCP provided internal feedback on ISO standards development for certain syringes. • OCP provided input into the 21st Century Cures Act and other innovative legislative initiatives relating to the regulation of combination products. • OCP participated in the Lean Management initiatives to revise standard operating procedures for jurisdiction assessments and the inter-Center consult requests/review process.
Continuing to actively participate in Agency information technology initiatives	OCP continued to coordinate and participate in cross-cutting information technology initiatives. Such initiatives are aimed at enhancing the infrastructure necessary to improve the efficiency, consistency, and reliability of information systems and communications within and among FDA medical product Centers and between FDA and combination product sponsors and other interested stakeholders.

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Appendix

Appendix A: FY 2015 Updated Performance Detail

The table below reflects the 341 original applications initially classified into one of nine categories of combination products received in FY 2015.

Workload by Combination Product Category Number

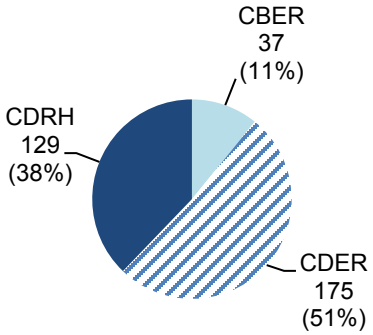
Application Type	1	2	3	4	5	6	7	8	9	Totals
Original NDAs	6	13	0	1	0	0	1	0	0	**21**
Original BLAs	0	0	4	0	0	0	0	0	0	**4**
Original PMAs	0	0	0	6	0	0	2	0	0	**8**
Original 510(k)s	8	0	0	57	0	0	5	1	8	**79**
Original INDs	9	50	18	4	4	40	3	48	5	**181**
Original IDEs	1	0	0	24	3	0	9	5	4	**46**
Original HDEs	0	0	0	0	0	0	2	0	0	**2**
Totals	**24**	**63**	**22**	**92**	**7**	**40**	**22**	**54**	**17**	**341**

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

Combination Product Applications (n = 341)



The pie chart to the right shows the number and percentage of combination product applications in FY 2015 by Center lead, as of September 30, 2016.

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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