FY 2017

PERFORMANCE REPORT TO CONGRESS

for the

Office of Combination Products

as required by the

Medical Device User Fee and Modernization Act of 2002

Report

The Food and Drug Administration's (FDA or the Agency) Fiscal Year (FY) 2017 Annual Report to Congress for the Office of Combination Products (OCP) includes data from the 14th 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 a drug, device, and/or biological product. 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 Centers, which can raise regulatory, policy, and review management challenges. Differences relating to the regulatory pathways and considerations for each type of constituent part (drug, device, biological product) 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 efficiency, consistency, transparency and predictability of the process for assigning combination products to the appropriate lead Center and for the regulatory 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. 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.

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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 2017 (October 1, 2016-September 30, 2017). OCP's activities and performance for FY 2017 that are highlighted in this report include:

- **Prompt Assignment of Combination Products**. In FY 2017, OCP continued to clarify the jurisdictional assignment of combination products and to provide prompt Request for Designation (RFD) decisions. OCP issued 5 combination products and 3 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 78 separate Pre-Request for Designation (Pre-RFD) submissions.[1] To enhance the RFD process, OCP in collaboration with the Office of Medical Products and Tobacco (OMPT), Center for Drug Evaluation and Research (CDER) Lean Enterprise Institute (LEAN) management mapping process, and the medical product Centers made some 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 these cooperative efforts. The revised process was communicated to stakeholders in a draft Pre-RFD guidance document issued in January 2017. In addition, to facilitate product classification and assignment, FDA issued a final guidance in September 2017, on classification of products as drugs and devices and additional product classification issues.

- **Timely and Effective Combination Product Review**. In FY 2017, OCP received 525 requests for product-specific assistance, the responses to which contributed to ensuring the timely and effective review of combination products. This is a 97 percent increase from the 266 requests received in 2016. OCP, in conjunction with the Centers and OMPT, identified mechanisms to improve the inter-center consult process. LEAN was utilized to analyze the then 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 was piloted through the end of FY 2017 and was expected to be fully implemented in light of the pilot results by early in FY 2018. 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,

[1] Informal requests for product classification and jurisdictional assessment/feedback are now referred to as "pre-RFDs" or pre-requests for designation.

identifying and resolving specific product issues, updating of the premarket review process, and developmental considerations for combination products.

FDA received 561 original premarket applications for combination products in FY 2017. This reflects a 69 percent increase from the 330 applications of the types reported in FY 2016 and the new inclusion in the FY 2017 report of data on two additional application types, abbreviated new drug applications and de novo classifications.[2] Inter-center consulting reviews for combination products increased to 1,419 for FY 2017 from 1,130 in FY 2016. 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 2017, OCP provided clarification and support for 74 separate postmarket matters. OCP continued to chair FDA working groups to address current good manufacturing practices (CGMPs) and postmarketing safety reporting (PMSR) requirements to combination products. FDA published a final rule on PMSR for combination products in December 2016, and a final guidance on CGMPs for combination products in January 2017. OCP also continued to work with the medical product Centers on registration and listing issues, postmarket manufacturing compliance, and other postmarket regulatory issues pertaining to specific combination products.

- **Procedural and Policy Activities and Accomplishments**. The Agency created a cross-cutting decisional Combination Products Policy Council (CPPC), consisting of senior leaders from all three medical product Centers, OMPT, Office of Special Medical Programs (OSMP), and OCP in FY 2016. The CPPC continued to provide direction regarding complex policy and procedural questions for combination products, relating to the implementation of section 3038 of the 21st Century Cures Act (the Cures Act), human factors, the inter-center consult process, availability of premarket pathways for combination products, and inter-component coordination on cross-cutting policy activities. 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 also continued to work with foreign counterparts, providing technical assistance and opportunities to foster regulatory convergence.

[2] FY 2016 numbers were changed to reflect updates to data presented in the FY 2016 OCP Performance Report. The updated data for FY 2016 is located in Appendix A.

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Acronyms

510(k) –Premarket Notifications

ANDA – Abbreviated New Drug Application

BLA – Biologics License Application

BSUFA – Biosimilar User Fee Act

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)

GDUFA – Generic Drug User Fee Act

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

Pre-RFD – Pre-Request for Designation

RFD – Request for Designation

SE – Substantially Equivalent

Introduction

On October 26, 2002, the Medical Device User Fee and Modernization Act (MDUFMA) was signed into law. 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 OCP within the Office of the Commissioner. On December 13, 2016, the Cures Act was signed into law. Among other things, the Cures Act clarified and expanded the duties of OCP, to include ensuring the alignment of premarket review of combination products. Information about OCP, including the authorizing text of MDUFMA as amended by the Cures Act, can be found on the OCP Web site at www.fda.gov/CombinationProducts/default.htm.

Description of Combination Products

Title 21 Code of Federal Regulations (CFR) § 3.2(e) states that combination products include:

(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 medical products (devices, drugs, and biological products) 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, applications of nanotechnology, and other innovative products and characteristics for diagnostic and therapeutic treatment of cardiovascular, neurological, metabolic, oncologic, and other disorders.

Statutorily Mandated Functions of OCP

MDUFMA and the Cures Act have established broad responsibilities for OCP that cover the regulatory life cycle from product jurisdiction decisions to duties relating to premarket review and postmarket oversight of combination products (i.e., drug-device, drug-biologic and device-biologic combination products). However, the primary responsibilities for scientific premarket review and postmarket regulation of combination products remain in the three medical product Centers – CBER, CDER, or CDRH – to which they are assigned by OCP.

Specifically, section 503(g)(8)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C 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 reviews and the alignment of agency feedback to the sponsor and by 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 stakeholders and works with the relevant Centers to develop guidance documents, regulations, processes, and procedures to clarify and enhance the efficiency, consistency and transparency of combination products regulation.

In addition, OCP has responsibility for FDA action on all requests for designation (RFDs) submitted by industry in accordance with 21 CFR Part 3, “Product Jurisdiction.” RFDs may request classification of a particular product as a biological product, device, or drug, or combination product, a determination of its Center assignment or both.

Performance Presented in This Report

This report presents FY 2017 OCP activities and accomplishments in assigning 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 combination product applications. Accordingly, this section also provides FY 2017 performance information and updates FY 2016 performance information as related to timeliness in days of the reviews of combination products in the subsection "Timely and Effective Premarket Review."[3]

Consistent with the mandated functions of OCP, information in this report 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, 2017.

[3] FDA has initiated various activities related to implementation of the Cures Act requirements for combination products, and this report has been modified to provide new information to reflect the Cures Act requirements and expectations. As the Cures Act implementation proceeds, the Agency will consider what additional information or adjustments may be appropriate for subsequent reports.

Prompt Assignment of Combination Products

OCP is required to respond to RFDs to classify a particular product as a biological product, device, drug, or combination product and to assign a particular product to the appropriate Agency component. OCP assigns primary jurisdiction for combination products (i.e., Center assignment) based on the product's primary mode of action (PMOA) (see 21 USC 353(g)(1), 21 CFR 3.4(b)) in response to RFDs. RFD submissions are subject to a statutory 60-day deadline.[4] OCP also provides responses to Pre-RFD requests for assistance regarding product classification and assignment.[5]

Requirement Workload Trends: FY 2012 to FY 2017

The number of classifications and assignments in FY 2017 is compared to the previous 5-year averages for the total number of combination product and non-combination product classification and assignment determinations in the table below. While the number of classifications and assignments increased compared to FY 2016, it is lower compared to the respective 5-year averages. Specifically, as compared to the previous 5-year average, the total number of RFD combination product classifications and assignments was 50 percent lower in FY 2017 and non-combination classifications and assignments was 63 percent lower for FY 2017.

RFD Determinations [6]

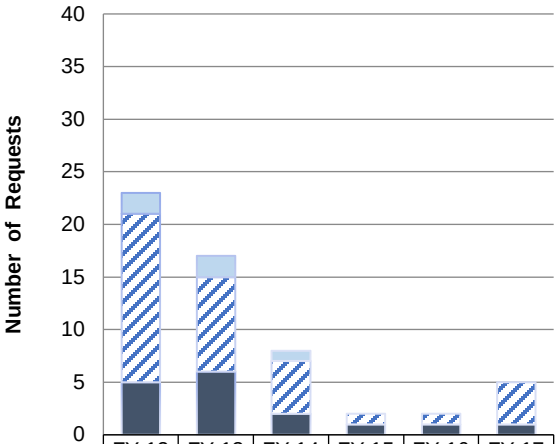
RFD Submissions	FY 12	FY 13	FY 14	FY 15	FY 16	FY 17	FY 12 to FY 16 5-Year Average	FY 17 Compared to 5-Year Average
Total RFD Combination Product Classifications/ Assignments	23	17	8	2	2	5	10	- 50%
Total RFD Non-Combination Product Classifications/ Assignments	10	14	9	7	2	3	8	- 63%

[4] OCP also provides assistance to sponsors regarding preparation of RFDs and development of data to support them, including in accordance with the Cures Act requirements codified at 21 USC 353(g)(1)(F).
[5] Responses to Pre-RFD submissions for product classification and jurisdictional assignments do not have a required timeframe. However, OCP attempts to respond to Pre-RFD submissions in a timeframe similar to RFDs (i.e., within 60 days). Information about Pre-RFD submissions (including the timeliness of OCP responses) is provided in section below titled Pre-RFD Workload Performance for FY 2017.
[6] 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 Workload Performance.

The total number of RFD combination product classifications and assignments issued in FY 2017 increased by 3 as compared to FY 2016.

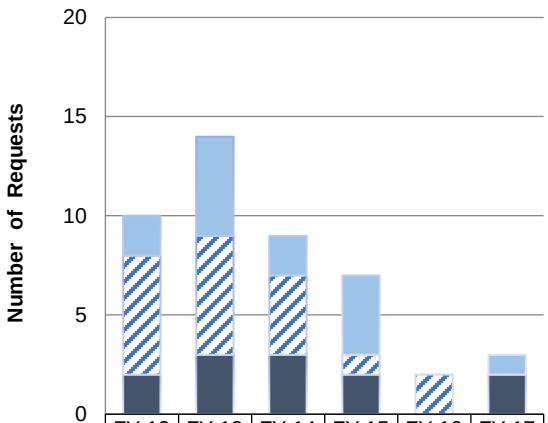
The total number of RFD classifications and assignments for non-combination products increased in FY 2017 by 1 compared to FY 2016.

Combination Product Assignment Requests



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

Non-Combination Product Assignment Requests



	FY 12	FY 13	FY 14	FY 15	FY 16	FY 17
Total	10	14	9	7	2	3
CBER	2	5	2	4	0	1
CDER	6	6	4	1	2	0
CDRH	2	3	3	2	0	2

OCP reviewed 61 RFD submissions in FY 2017.[7] Of these submissions, decisions were issued for 8 submissions (13 percent), 49 RFD submissions were found by OCP to have insufficient information for filing (80 percent), and 4 submissions were withdrawn by the sponsor prior to filing or issuance of a decision (7 percent).

In FY 2017, the 8 RFD determinations for combination (5) and non-combination (3) products, were all issued by the statutorily mandated 60-day deadline. The average and median combination product RFD review time was 58 days. The average non-combination product RFD review time was 57 days, with a median review time of 58 days. The following tables provide timeliness data by product type of the issued RFD decision.

Timeliness of Combination Product Determinations

Determination	Product Assignments Issued*	Percent On Time*
Drug-Device	5	100%
Drug-Biologic	0	NA
Device-Biologic	0	NA
Drug-Device-Biologic	0	NA
Total	**5**	**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 combination product in FY 2017.

Timeliness of Non-Combination Product Determinations

Determination	Product Assignments Issued*	Percent On Time*
Drug	0	NA
Biologic	1	100%
Device	2	100%
Total	**3**	**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 2017.

Pre-RFD Workload Performance

In addition to RFDs, OCP also provided preliminary feedback/assessments in response to Pre-RFD submissions for product classification and jurisdictional assignment in FY 2017. The Pre-RFD process may be preferable to the more formal RFD process, such as 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), when a sponsor is contemplating whether to develop a specific product, or what configuration of that product to pursue. In the tables below, OCP Pre-RFD submission review workloads in FY 2017 are provided. FY 2017 is the first full year of the "formalized" Pre-RFD program.[8] As such, available data allowing for a year-to-year comparison are not yet available. However, this year-to-year comparison data will be provided in future reports as it becomes available.

[7] Of these 61 submissions, 59 submissions were received in 2017 and two submissions were carried over as pending at the end of FY 2016. Regarding the FY 2016 pending RFDs, 1 RFD resulted in a decision and 1 RFD was withdrawn by the sponsor prior to filing.

[8] Formalization of the Pre-RFD program as a distinct OCP activity occurred during FY 2016. Consistent with past practice, Pre-RFD data presented in the FY 2016 report continued to be grouped with center-requested consultations (i.e., product classification and jurisdictional requests that originate with the FDA Centers and not with product sponsors). However, Pre-RFDs and Center requested consultations are two different types of interactions with OCP. Therefore, these two different data groups will be reported independently going forward. Center-requested consultations are discussed in the following section.

In FY 2017, 78 Pre-RFD assessments were issued for combination (44) and non-combination (34) products, 96% by OCP's internally established 60-day goal[9] (see following tables). In FY 2017, the 60-day review goal was missed for 3 submissions out of a total of 78. The average assignment review time was 37 days, with a median review time of 47 days. The following tables show Pre-RFD feedback for combination products and non-combination products based on classification and Center assignment.

OCP Pre-RFD Submission Workload

Pre-RFD Assessments	FY 17
Combination Product Assessments	44
Non-Combination Product Assessments	34
Total Pre-RFD Assessments	78

Number of Combination Product Pre-RFD Assessments

Classification	Assignments Issued	Percent Issued in 60 Days
Drug-Device	35	100%
Drug-Biologic	1	100%
Device-Biologic	5	100%
Drug-Device-Biologic	2	50%
Unclassified	1	100%
Total	**44**	**98%**

Number of Combination Product Pre-RFD Assessments by Center Assignment

Center Assignment	Consultations Issued
CDER	32
CBER	5
CDRH	7
Total	**44**

[9] OCP does not have a mandated review timeframe for Pre-RFD assessments. However, OCP attempts to review Pre-RFD assessments within the same timeframe as RFD submissions (i.e., 60 days).

Number of Non-Combination Product Pre-RFD Assessments

Classification	Assignments Issued	Percent Issued in 60 Days
Drug	10	100%
Biologic	5	100%
Device	19	89%
Total	**34**	**94%**

Number of Non-Combination Product Pre-RFD Assessments by Center Assignment

Center Assignment	Consultations Issued
CDER	13
CBER	7
CDRH	14
Total	**34**

OCP Performance on Internal Center-Requested Classification and Assignment Consultations

In addition to RFDs and Pre-RFDs submitted by industry/sponsors, OCP also provided classification and assignment feedback for combination and non-combination products in response to requests from Centers in relation to premarket submissions. FDA review Centers may contact OCP for assistance in determining if the product submitted to a Center for review is appropriately assigned to that Center or whether the sponsor would need to be referred to OCP for a classification or assignment determination, or both. The number of such consultations provided by OCP is presented in the table below. As with the Pre-RFD data presented above, FDA intends to provide in future reports metrics for multiple fiscal years, as such data become available.

Center-Requested Classification and Assignment Consultations

Center Assignment	Consultations
CDER	29
CBER	3
CDRH	16
Total	**48**

Additional OCP Classification and Assignment Activities

This reporting category reports on all other activities not falling within the classification and assignment activities reported above. Examples of this category of activity include questions to OCP about process (e.g., how to prepare an RFD or Pre-RFD) and consultations from FDA Centers where OCP recommended sponsor referral to OCP for further discussion.

Additional Number of OCP Product Classification and Assignment Activities

	FY 17
Jurisdiction/Classification Issues	528

OCP Requirements and Accomplishments

Type of Activity	FY 2017 Accomplishments
Issuing required RFD assignments within 60 days	OCP issued all RFD assignments by the statutory 60-day determination deadline.
Clarifying standards for product classification and preparing guidance on this issue	OCP published a final guidance on the classification of drugs and devices and associated considerations, including for combination products. OCP also 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 for challenging categories of products, and continued to pursue and support related policy initiatives, including issuance of guidance on classification of human tissue products t, and to clarify standards for cross-labeled combination product status.
Enhancing the timeliness, consistency, and clarity of jurisdictional decisions across FDA	OCP continued to facilitate product classification and jurisdictional meetings with CBER, CDER, and CDRH and Counsel OCC staff, to exchange information and discuss challenging product classification and 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 assignment. See also discussion of issuance of guidance on the Pre-RFD program and classification of products and other policy activities relating to product classification and assignment under Policy Activities and Accomplishments

Combination Product Pre-Market Review

OCP is responsible for ensuring the timely, effective and aligned premarket review of combination products, including by overseeing the timeliness of reviews and the alignment of feedback by 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 biological products. 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.[10]

In FY 2017, in light of feedback from stakeholders and internal FDA staff regarding the consistency, efficiency, and coordination within FDA of premarket reviews for combination products, FDA piloted a revised inter-center consultative process to ensure consultation occurs as appropriate, improve early identification of the inter-center review team, enhance efficiency of consult request issuance and clarity of questions asked, and better ensure responsiveness and documentation of completed consults. Based on the results of this pilot, an updated process is expected to be implemented and incorporated into the FDA Staff Manual Guide by early FY 2018.

Number and Types of Combination Products Submitted for Review

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

- Data on the number and types of combination products submitted for review for FY 2017 by CBER, CDER, and CDRH include submissions filed or received in FY 2017.
- When reporting timeliness in days for the review for CBER-led or CDER-led combination products, The prescription Drug User Fee Act (PDUFA V) goals were referenced for priority and standard new drug applications (NDAs) and applicable biologics license applications (BLAs), the Generic Drug User Fee Act (GDUFA) goals were referenced for 2017 goals for abbreviated new drug applications (ANDAs), and Biosimilar User Fee Act (BsUFA) goals were referenced for 2017 goals for BLAs for biosimilar combination products. For 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.
- 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).

[10] In FY 2017, the inter-center consultation process is undergoing a review and testing enhancements. Additional information regarding these changes is available on pages 17 and 18 of the report.

- 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 2012 to FY 2017

Beginning with FY 2017, FDA is now reporting on workload for abbreviated new drug applications (ANDAs) and de novo classifications (de novos) submissions in addition to the previous application types reported upon in prior OCP Reports to Congress. FDA is also tracking user fee performance for biosimilar products separately from other biological products. FDA is making these changes in light of submission trends and clarification provided by Cures with respect to premarket availability of premarket pathways for combination products.

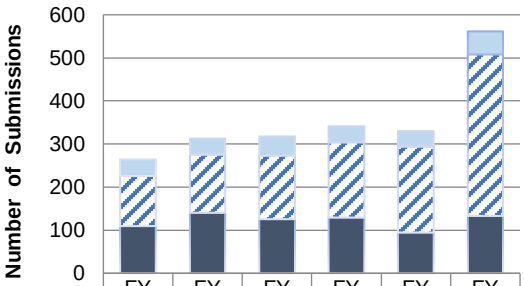
FY 2017 Submission Review Workloads

Submission/Request	FY 12	FY 13	FY 14	FY 15	FY 16*	FY 17[11]
Total Combination Products Submitted for Review by Centers	264	313	317	341	330	561

* FY 2016 numbers were changed to reflect updates to data presented in the FY 2016 OCP Performance Report.

The total number of combination products submitted for review increased in FY 2017. Sixty-seven percent (67%) of the combination product submissions received were led by CDER, followed by CDRH (24 percent) and CBER (9 percent).

Combination Product Application Submissions



	FY 12	FY 13	FY 14	FY 15	FY 16	FY 17
Total	264	313	317	341	330	561
CBER	38	37	44	37	36	53
CDER	117	136	147	175	199	375
CDRH	109	140	126	129	95	133

[11] Reported FY 2017 data include additional submission types (i.e., ANDAs and de novo submissions) that were not previously reported in past years. As such the data shown for FY 2017 are not directly comparable to the past years shown in this table.

The table below presents the 561 original applications for combination products received in FY 2017, broken down by the identified ten application types and by the product's initial classification into one of nine categories of combination product.[12] The same table reflecting applications received in FY 2016 is updated in Appendix A to reflect corrections and actions as of September 30, 2017. The majority of the applications (53 percent) received in FY 2017 were Original INDs, followed by Original 510(k)s (16 percent) and ANDAs (12 percent). The most common combination product category was pre-filled drug delivery device/system (19 percent), followed by device coated/impregnated/otherwise combined with drug (18 percent).

Workload by Combination Product Category Number

Application Type	1	2	3	4	5	6	7	8	9	Totals
Original NDAs	7	23	0	2	0	0	0	0	2	**34**
Original BLAs	0	0	8	0	0	1	0	0	0	**9**
Original PMAs	0	0	0	5	1	0	1	0	2	**9**
Original 510(k)s	6	0	2	56	3	0	7	3	12	**89**
Original INDs	33	46	23	12	14	66	0	92	11	**297**
Original IDEs	6	0	0	27	0	0	4	3	7	**47**
Original HDEs	0	0	0	0	0	0	0	0	0	**0**
ANDAs	27	40	0	0	0	0	0	0	1	**68**
Biosimilars	6	0	1	0	0	0	0	0	0	**7**
De novos	1	0	0	0	0	0	0	0	0	**1**
Totals	**85**	**109**	**34**	**102**	**18**	**67**	**12**	**98**	**35**	**561**

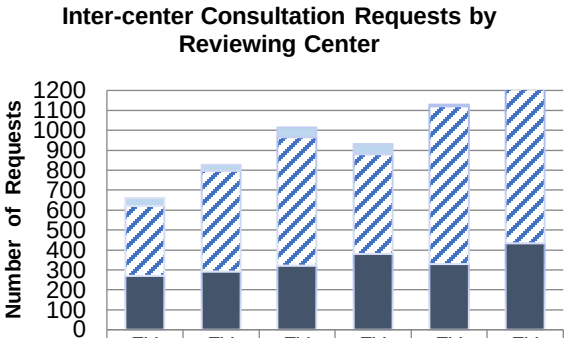
Combination Product Category Key:

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).

Inter-center Consultation Requests

The total number of inter-center consult requests increased for FY 2017 to the highest number in the past 6 years. The number of inter-center consults increased by 55% as compared to the previous 5-year average.



	FY 12	FY 13	FY 14	FY 15	FY 16	FY 17
Total	660	828	1,013	932	1,130	1,419
CBER	40	31	48	53	9	105
CDER	350	506	643	499	793	881
CDRH	270	291	322	380	328	433

Total review workload for inter-center consults in FY 2017 is compared to the previous 5-year averages in the table below.

FY 2017 Inter-center Consult Workloads

Submission/Request	FY 12	FY 13	FY 14	FY 15	FY 16*	FY 17	FY 12 to FY 16 5-Year Average	FY 17 Compared to 5-Year Average
Total Inter-center Consult Requests	660	828	1,013	932	1,130	1,419	913	+ 55%

The table below presents the number of inter-center consult requests during FY 2017, broken down by requesting Center (i.e., primary assigned lead Center) and which Center reviewed the consult (i.e., consulting center).[13]

Number of Premarket Review Inter-center Consults for Combination Products by Requesting and Assigned Center

Requesting Center	Reviewing Center			
	CBER	CDER	CDRH	Number of Consults
CBER	--	10	6	16
CDER	30	--	427	457
CDRH	75	871	--	946
Total	**105**	**881**	**433**	**1,419**

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 New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), Prescription Drug User Fee Act (PDUFA) Biologics License Applications (BLAs), Biosimilar User Fee Act (BsUFA) BLAs, Premarket Approval Applications (PMAs), Device Classification under Section 513(f)(2) of FD&C Act (De Novos), and Premarket Notifications (510(k)s). PDUFA V, Generic Drug User Fee Act (GDUFA), BsUFA, and Medical Device User Fee Amendments (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 timeframe. 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.

[13] Some applications were associated with multiple consulting requests. Additionally, because these consulting requests are associated with any combination product under review, 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 2017 (reported in the previous section).

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	Standard with no Advisory Committee Input	180 days
MDUFA III	Expedited and Original PMAs	Standard with Advisory Committee Input	320 days
MDUFA III	510(k)s	Standard	90 days
MDUFA III	BLAs	Priority	6 months
MDUFA III	BLAs	Standard	10 months
BsUFA	Biosimilars	Standard	10 months
GDUFA I	ANDAs	Standard	10 months
MDUFA III	De Novos	Standard	N/A

[†] 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).

FDA premarket review performance information 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 2016 combination product submissions and presents FDA's review performance on the FY 2017 combination product submissions through September 30, 2017.

FY 2016 and FY 2017 Review Performance

Final FY 2016 review goal performance is presented in the table below and were similar between FY 2016 and FY 2017.

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	183	165 to 336
NDAs	Standard	10 months	16	304	301 to 394
BLAs	Priority	6 months	2	289	242 to 335
BLAs	Standard	10 months	6*	351	301 to 457
Expedited and Original PMAs	Standard	180 or 320 days†	2*	177	177
510(k)s	Standard	90 days	67*	87	9 to 161

* FY 2016 numbers were changed to reflect updates to data presented in the FY 2016 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 2017 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	4	184	182 to 184
NDAs	Standard	10 months	30*	304	276 to 365
BLAs	Priority	6 months	4*	240	239 to 240
BLAs	Standard	10 months	5*	363	363
Expedited and Original PMAs	Standard	180 or 320 days†	9*	179	170 to 180
510(k)s	Standard	90 days	78*	81	15 to 220
Biosimilars	Standard	10 months	7*	302	302
ANDAs	Standard	10 months	67*	301	267 to 316
De Novos	Standard	N/A‡	1	126	126

* Included in this count are NDAs, ANDAs, BLAs, PMAs 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 reported 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.

‡ De Novo applications did not have an associated performance goal in FY17.

Premarket Review

OCP continued to facilitate the premarket review of combination products that raised complex regulatory issues. OCP fosters early interactions between industry and FDA to develop clearly delineated regulatory pathways for the development of combination products and expeditious review of premarket submissions for these products. Responding to requests from both industry and FDA review staff, OCP provides guidance on regulatory challenges unique to combination products. OCP also serves as a resource for FDA staff on the appropriate use and interpretation of combination product categorization for premarket submissions and assists staff in CBER, CDER, and CDRH in determining the correct combination product categories for data reporting purposes. Finally, OCP leads or participates in meetings and discussions, and otherwise engages, to ensure efficient, effective communication between sponsors and FDA review staff. OCP FY 2017 accomplishments related to premarket review are included in the tables below.

Number of OCP Documented Premarket Activities

	FY 12	FY 13	FY 14	FY 15	FY 16	FY 17	FY 12 to FY 16 5-Year Average	FY 17 Compared to 5-Year Average
Premarket Review Issues	120	157	402	225	266	525	234	+ 124%

OCP received 525 requests for product-specific assistance, the responses to which contributed to ensuring the timely, effective and aligned review of combination products. OCP addressed issues related to novel drug and biological product delivery systems, emergency use products, generic products that include devices, alignment of preclinical and biocompatibility data requests, approvability of rare disease products, alignment of review assessments for drug-pump delivery and drug-device implant products, consistency and clarity of labeling, and developmental considerations for combination products with mobile communication technologies.

OCP oversees inter-center consults and facilitates inter-center coordination and Agency coordination with sponsors, to ensure that reviews of premarket applications are coordinated as appropriate, completed in a timely manner and meet PDUFA V, GDUFA I, BsUFA I, 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; resolves other barriers to timely completion of consults.

In addition, OCP provided assistance to the Centers in resolving regulatory and scientific issues relating to specific combination products or to specific categories of combination products. OCP also responds to industry inquiries. For example, OCP responded to external industry requests to host cross-center early development meetings on bundled issues to minimize redundant product meetings.

Type of Activity	FY 2017 Accomplishments
Providing Significant Premarket Review 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 conditions of use • Medical imaging drugs with device delivery systems and imaging systems • Coordination of premarket CGMP inspections • Application of 21 CFR Part 4 to premarket submissions under review • Inter-center manufacturing process compliance and safety evaluator processes • Registration and listing and associated information technology infrastructure 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 for a combination product • Unique device identifiers and standardized numerical identification • Alignment of IND and IDE requirements for combination products • Coordination of cross-center safety signal assessments

Combination Product Postmarket Activities

OCP is tasked with ensuring the consistency and appropriateness of postmarket regulation of combination products, and FDA is required to describe any improvements in the consistency of postmarket regulation of combination products.

OCP meets the requirement to ensure consistency and appropriateness 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 (as discussed more fully in Policy Activities and Accomplishments below), 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 on CGMP facility inspection issues and on seizure of products at ports of entry to stop illegal products from entering the United States; responding to product defect issues; providing assistance on enforcement issues relating to import requirements and assisting in the development of compliance and enforcement action communications such as warning letters. OCP FY 2017 accomplishments related to the consistency and appropriateness of postmarket regulation are included in the table below (see also Policy Activities and Accomplishments below).

Documented Product-Specific Postmarket Regulatory Activities

	FY 12	FY 13	FY 14	FY 15	FY 16	FY 17	FY 12 to FY 16 5-Year Average	FY 17 Compared to 5-Year Average
Postmarket Regulatory Activities	33	57	110	71	50	74	64	+16%

OCP addressed 74 postmarket-related matters involving such issues as the application of CGMPs and quality system regulations for inspections of combination products, appropriate mechanisms and responsibilities for reporting adverse events, and requirements for registration and listing. This represents a 16% increase in the number of issues compared to the prior 5-year average.

These efforts have helped improve the consistency of postmarket regulation in a number of ways, including by:

- Enhancing coordination among Agency components in support of CGMP inspectional and compliance policies and practices
- Clarifying stakeholder and FDA understanding of CGMP obligations (see also publication of a final guidance discussed under Policy Activities and Accomplishments below)
- Clarifying stakeholder and FDA understanding of PMSR requirements (see also publication of a final rule discussed under Policy Activities and Accomplishments below)

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).

Percentage of Combination Products for which a Dispute Resolution was Requested

FDA is required to identify the percentage of combination products for which a dispute resolution, with respect to premarket review, was requested by the combination product's sponsor.[14] For FY 2017, the percentage is zero. The "Timely and Effective Premarket Review" section of this report provides examples of informal facilitation and resolution of issues related to premarket review.

[14] This reporting requirement was established by the Cures Act and replaces the prior requirement to report on the timeliness in days of dispute resolutions regarding combination products.

Policy Activities and Accomplishments

Regulatory Initiatives

OCP activities include leading and assisting with policy initiatives important to and affecting the regulation of combination products. Examples of such activities pursued in FY 2017 are discussed below and included in the following tables.

Supporting legislative initiatives

OCP participated in development of FDA positions and engagement with Congress and stakeholders regarding legislative initiatives and briefings on combination products and combined use of medical products, including:

- The Cures Act and
- Fostering Innovation in Medical Imaging Act of 2017

Streamlining regulation

OCP published a final rule on PMSR for combination products to clarify and streamline PMSR requirements for combination products subject to premarket review.

OCP initiated revisions to FDA's jurisdiction regulations at 21 CFR Part 3, to update and clarify them in light of legislative and other policy developments.

Providing clarifying guidance

OCP published with the medical product Centers:

- Final guidance on current good manufacturing requirements for combination products[15]
- Final guidance on classification of products as drugs and devices and additional classification issues[16]
- Draft guidance on the Pre-RFD Program[17]

[15] Available at https://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm.
[16] Available at https://www.fda.gov/RegulatoryInformation/Guidances/ucm258946.htm.
[17] Available at https://www.fda.gov/RegulatoryInformation/Guidances/ucm534661.htm.

Additional Jurisdictional Regulatory Initiatives

Type of Activity	FY 2017 Accomplishments
Developing regulations	Additional OCP jurisdiction-related activities included participating in the following Agency rulemaking and guidance initiatives: • Rulemaking on the regulatory status of wound care products • Rulemaking on the meaning of "protein" in the definition of "biological product" in the Public Health Services Act
Participation in other inter-center and Agency-wide working groups to clarify issues related to product jurisdiction	OCP jurisdiction-related activities included participating in the following Agency rulemaking and guidance initiatives: • Enhancing the efficiency and transparency of the Pre-RFD Program • Classification-related issues for e-cigarettes and products that include tobacco, drugs, and devices

Additional Premarket Review Regulatory Initiatives

Type of Activity	FY 2017 Accomplishments
Developing guidance and regulations	• OCP chaired a cross center working group to finalize guidance on human factors studies for combination products • OCP chaired a cross-center working group to begin development of draft guidance for technical aspects of intravaginal ring drug-delivery combination products OCP participated in the development of: • rulemaking on De Novo classification • rulemaking on use of symbols in device and device-led combination product labeling • Guidance on pre-submission facility inspection for generic drugs • Guidance on metered dose inhalers and dry powder inhalers • Guidance on flow restrictors • Guidance and citizen petition responses for specific types of generic combination products • Guidance on comparative assessments, including human factors for generic drug-led and interchangeable biologic-led combination products • Selection of appropriate package type terms and recommendations for labeling injectable medical products • Where to provide device constituent part information when using the CDER/CBER Electronic Common Technical Document (eCTD) format • Technical considerations for visual inspection for particulates in injectable solutions • Final guidance on classification of human tissue products • Comments on ISO standards development for certain syringes

Type of Activity	FY 2017 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 complex legal and public health issues associated with the marketing of products intended for use with other legally marketed products, including preparations for a Part 15 hearing
Participation in other inter-center and Agency-wide working groups to clarify issues related to combination products	OCP led or participated in working groups with Centers and other Agency components regarding: • The appropriate regulatory pathway for novel technology diagnostics and biomarkers for use with drug or biological products • Companion diagnostics • Expanding non-prescription drug availability • Development of Agency thinking on regulation of software as drug labeling Agency-wide working groups such as FDA's Task Force on Antimicrobial Resistance
Consultative/Collaborative Review Process and Procedures Development	OCP along with other components of the Office of the Commissioner and with the medical product Centers continued an inter-center consult process pilot intended to enable timely and consistent coordination to enable efficient, consistent review of submissions. This activity included development and presentation of training materials; facilitating, monitoring and assessing consult activities

Additional Postmarket Review Regulatory Initiatives

Type of Activity	FY 2017 Accomplishments
Participation in other inter-center and Agency-wide working groups to clarify issues related to combination products and guidance development	• OCP continued to chair working groups relating to PMSR for combination products, focused on development of a draft guidance regarding the final rule and other efforts to implement the rule including development of internal SOPs • OCP 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, which was published by AAMI in 2017, and that began work on a TIR on risk management for combination products. • OCP continued to chair a working group and leadership body to support implementation of the final rule on CGMPs for combination products, including inspectional activities and expectations relating to premarket submissions • OCP continued to work with Centers on track and trace regimes with respect to combination products, including Unique Device Identifier, numeric drug coding and serialized numeric identifiers

Additional Activities and Accomplishments

Information Technology

OCP continued to coordinate and participate in cross-cutting information technology initiatives, to enhance infrastructure and update guidance as appropriate to improve the efficiency, consistency and reliability of information systems and communications within and among medical product Centers and between FDA and combination product sponsors and other interested stakeholders. OCP led efforts to improve staff access to IT systems needed for the review of combination products, and to update PMSR Agency IT systems and develop new guidance on how stakeholders should engage with them, in light of the final rule on PMSR for combination products.

External Outreach

OCP conducts outreach activities to share information on FDA assignment and regulation of combination products by meeting with trade associations and coalitions (e.g., Combination Products Coalition, Advanced Medical Technology Association, Association for Advancement of Medical Instrumentation) representing the drug, device, biological product, and combination product industries, and participating in industry conferences. Discussions and presentations focus on a wide range of topics, including emerging issues in combination product regulation, the role of OCP, policies and guidances under consideration, rulemaking, specific categories of combination products, particular regulatory issues, and stakeholder priorities for further action. Examples of FY 2017 outreach activities are included in the table below.

Type of Activity	FY 2017 Accomplishments
Presentations and outreach activities	OCP participated in a number of outreach activities. The following are examples of 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 • 2017 Drug Information Association Annual Conference on Combination Products • Parenteral Drug Association/FDA Joint Regulatory Conference • Drug Information Association Annual Meeting 2017 • FDLI 2017 Annual Conference • Xavier University Health Combination Products Summit (September 2017)

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Appendix

Appendix A: FY 2016 Updated Performance Detail

The table below reflects the 331 original applications initially classified into one of nine categories of combination products received in FY 2016.

Workload by Combination Product Category Number

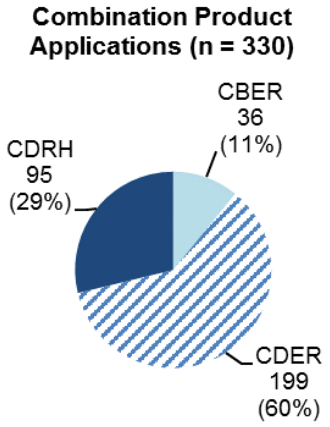
Application Type	1	2	3	4	5	6	7	8	9	Totals
Original NDAs	5	12	0	1	0	0	0	0	1	**19**
Original BLAs	1	0	6	0	1	0	0	0	0	**8**
Original PMAs	0	0	0	2	0	0	0	0	0	**2**
Original 510(k)s	10	0	0	51	1	0	5	1	3	**71**
Original INDs	5	50	10	11	1	40	1	79	4	**201**
Original IDEs	3	0	0	11	4	0	1	5	5	**29**
Original HDEs	0	0	0	0	0	0	0	0	0	**0**
Totals	**24**	**62**	**16**	**76**	**7**	**40**	**7**	**85**	**13**	**330**

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 2016 by Center lead, as of September 30, 2017.



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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