FY 2019

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 fiscal year 2019 annual performance report to Congress for the Office of Combination Products (OCP) in the U.S. Food and Drug Administration (FDA). This report includes data from the 16th full year since OCP was established, as mandated by the Medical Device User Fee and Modernization Act of 2002 (P.L. 107-250), 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 among FDA's human medical product Centers, which include the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and the Center for Devices and Radiological Health. Combination products involve constituent parts that would usually 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 the considerations for each type of constituent part (i.e., drug, device, and/or biological product) can impact the regulatory processes for all aspects of combination product development and management, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, user fees, and postapproval 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 acts to facilitate interactions between industry and FDA to clearly delineate regulatory pathways, monitor and adjust processes to ensure a timely and effective premarket review, and help ensure a consistent and appropriate postmarket regulation of combination products. In addition to combination products, OCP has classification and assignment responsibilities for non-combination drug, device, and biological 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.

Stephen M. Hahn, M.D.
Commissioner Food and Drugs

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Executive Summary

The U.S. Food and Drug Administration (FDA or the Agency) established the Office of Combination Products (OCP) on December 24, 2002, as required by the Medical Device User Fee and Modernization Act of 2002 (P.L. 107-250). 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's Centers; the timely, effective, and aligned premarket review of applications for these products; and the consistent and appropriate postmarket regulation of these products subject to the relevant statutory requirements to the extent permitted by law.

This report presents OCP's annual performance report to Congress and covers activities and accomplishments during fiscal year (FY) 2019 (i.e., October 1, 2018 to September 30, 2019). OCP's activities and performance for FY 2019 that are highlighted in this report include:

1. **Prompt Assignment of Combination Products.** In FY 2019, OCP continued to clarify the classification and jurisdictional (i.e., Center) assignment of medical products and to provide prompt Request for Designation (RFD) decisions. OCP issued seven combination product and six non-combination RFD decisions, with every classification and/or assignment decision meeting the 60-day statutory decision time requirement. Refer to Tables 1-3 for trending data from FY 2014 through FY 2019. OCP also provided timely classification and jurisdictional feedback for 83 separate Pre-Request for Designation submissions. OCP issued 94 percent of Pre-RFD by OCP's internally established 60-day goal date, a slight decrease from 98% in 2018 and 96% in 2017. For trending data from FY 2017 through FY 2019, view Table 6.

2. **Timely and Effective Combination Product Review.** In FY 2019, OCP received 144 requests for product-specific assistance, the responses to which contributed to ensuring the timely and effective review of combination products. There was a 59 percent decrease from the number of requests received in FY 2019 compared to the 5-year average (i.e., from FY 2014 to 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, updating the premarket review process, and addressing developmental considerations for combination products.

    a. FDA received 518 original premarket applications for combination products in FY 2019. This reflects a 33 percent increase from the 390 original premarket applications reported in FY 2018.[1] Inter-Center consulting reviews for combination products decreased to 1,328 for FY 2019 from 1,445 in FY 2018. Examples of combination product types can be found on the Combination Products web site.[2]

[1] FY 2018 numbers have been changed to reflect updates to the data presented in the FY 2018 OCP performance report. The updated data for FY 2018 are located in Appendix A.
[2] Available at www.fda.gov/CombinationProducts/default.htm.

3. **Consistent and Appropriate Postmarket Regulation**. In FY 2019, OCP provided clarification and support for 62 separate postmarket matters. OCP continued to chair FDA working groups to address current good manufacturing practices and postmarketing safety reporting (PMSR) requirements for combination products. Notably, FDA published a final guidance in July 2019[3] to help implement its December 2016 final rule on PMSR for combination products.[4] In addition, OCP worked with other Agency components to enhance training, databases, and resources to support postmarket inspectional and related manufacturing compliance oversight and to support implementation of the 2016 PMSR rule in anticipation of compliance enforcement dates in July 2020 and 2021.[5] 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.

4. **Procedural and Policy Activities and Accomplishments**. In FY 2019, the cross-cutting decisional Combination Products Policy Council consisting of senior leaders from all three human medical product Centers, the Office of Clinical Policy and Programs, and OCP continued to provide direction regarding complex policy and procedural questions for combination products, other medical products intended for combined use, and the classification and assignment of medical products. Topics addressed included implementation of section 3038 of the 21st Century Cures Act, human factors, the inter-Center consult process, the availability of premarket pathways for combination products, the inter-component coordination on combination product policy activities, and regulatory considerations for cross-labeled and other separately distributed medical products intended for combined use. Among other efforts, in FY 2019, OCP worked with the human medical product Centers to issue one proposed rule, five final guidances, and six draft guidances relating to combination products and combined use of medical products. OCP also continued to conduct external outreach activities through a variety of educational and informational presentations to national and international audiences, presenting at eleven conferences during the fiscal year. These activities were intended to foster greater efficiency, consistency, and transparency of the combination product development and premarket review process by enhancing understanding of both the complex regulatory and scientific issues that arise regarding combination products and how to work with FDA to address these issues.

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[3] See https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarketing-safety-reporting-combination-products.
[4] See https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.
[5] See the immediately in effect guidance for industry and Food and Drug Administration staff *Compliance Policy for Combination Product Postmarketing Safety Reporting* (April 2019), available at https://www.fda.gov/media/111795/download.

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Abbreviations

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

DIA – Drug Information Association

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

IT – information technology

MDUFA – Medical Device User Fee Amendments

MDUFMA – Medical Device User Fee and Modernization Act of 2002

NDA – new drug application

OCC – Office of the Chief Counsel

OCP – Office of Combination Products

PDUFA – Prescription Drug User Fee Act

PMA – premarket approval application

PMOA – primary mode of action

PMSR – postmarketing safety reporting

Pre-RFD – Pre-Request for Designation

RFD – Request for Designation

SMG – Staff Manual Guide

SOP – standard operating procedure

Introduction

On October 26, 2002, the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) (P.L. 107-250) was signed into law. Among other things, MDUFMA required the U.S. Food and Drug Administration (FDA or the Agency) 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 like products to the extent permitted by law." In response, FDA established the Office of Combination Products (OCP) within the Office of the Commissioner. On December 13, 2016, the 21st Century Cures Act (Cures Act) was signed into law. Among other things, section 3038 of the Cures Act clarified and expanded the duties of OCP to include ensuring the alignment of the 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 Combination Products web site.[6]

Description of Combination Products

Title 21 of the Code of Federal Regulations (CFR) (section3.2(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 are physically, chemically, or otherwise combined or mixed and produced as a single entity;

(2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

(3) A drug, device, or biological product packaged separately that, according to its investigational plan or proposed labeling, is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; 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.

[6] Available at www.fda.gov/CombinationProducts/default.htm

Some combination products have the potential to provide enhanced therapeutic advantages compared to non-combination medical products (i.e., 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.

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 the premarket review and postmarket oversight of combination products. However, the primary responsibilities for the scientific premarket review and the postmarket regulation of combination products remain in the three human medical product Centers – 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) – to which they are assigned by OCP.

Specifically, section 503(g)(8) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353 (g)(8)) 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 the Agency's feedback to the sponsor and by coordinating reviews involving more than one Center;

(3) Ensure the consistency and appropriateness of the postmarket regulation of like products subject to the same statutory requirements to the extent permitted by law;

(4) Resolve disputes regarding the timeliness of the premarket review of combination products; and

(5) Review and modify/revise/eliminate, as needed, 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's 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 the Agency's regulation of combination products.

In addition, OCP has responsibility for FDA's actions on all Requests for Designation (RFDs) submitted by industry in accordance with 21 CFR part 3, "Product Jurisdiction." RFDs may request (1) a classification of a particular product as a biological product, device, or drug or as a combination product, (2) a determination of its Center assignment or both, or both (1) and (2). RFDs provide a formal legally binding classification and Center assignment response.

Performance Presented in This Report

This report presents OCP's FY 2019 activities and accomplishments. There are key measures included in this report that should be made public. These reportable measures support the mandated functions of OCP. Specifically, this report presents information and data on OCP's activities related to the following:[7]

- 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

Percentage of combination products for which a dispute resolution, with respect to premarket review, was requested.

Unless otherwise noted, all performance data are as of September 30, 2019.

[7] FDA has initiated various activities related to its implementation of the Cures Act's requirements for combination products, and this report has been modified to provide new information to reflect the Cures Act's 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 Center (i.e., CBER, CDER, or CDRH). OCP assigns the primary jurisdiction for combination products (i.e., the Center assignment) based on the product's primary mode of action (PMOA) (see 21 U.S.C 353(g)(1) and, 21 CFR 3.4(a)) in response to RFDs. RFD submissions are subject to a statutory 60-day deadline for FDA response.[8] OCP also provides responses to Pre-Request for Designation (Pre-RFD) requests for assistance regarding product classification and assignment.[9]

Requirement Workload Trends: FY 2014 to FY 2019

In the table below, the total number of RFD determinations (i.e., classifications and assignments for both combination and non-combination products) in FY 2019 is compared to the previous 5-year averages. The total number of RFD determinations in FY 2019 increased by 63 percent compared to FY 2018. RFD determinations for combination products were 40 percent higher than the average for the previous 5 years, and RFD determinations for non-combination products were 50 percent higher over this 5-year average.

Table 1. RFD Determinations from FY 2014 to FY 2019 [10]

RFD Submissions	FY 14	FY 15	FY 16	FY 17	FY 18	FY 19	FY 14 to FY 18 5-Year Average	FY 19 Compared to 5-Year Average
Total RFD Combination Product Classifications/ Assignments	8	2	2	5	8	7	5	+40%
Total RFD Non-Combination Product Classifications/ Assignments	9	7	2	3	0	6	4	+50%

[8] OCP also provides assistance to sponsors regarding the preparation of RFDs and works with sponsors who disagree with FDA's classification or assignment determination on potential studies to support a change to the determination (21 U.S.C. 353(g)(1)(F)).

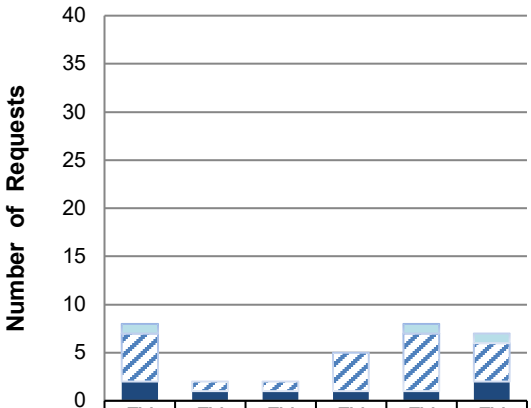
[9] Responses to Pre-RFD submissions for product classification and jurisdictional assignments do not have a required time frame. However, OCP attempts to respond to Pre-RFD submissions in the same time frame as RFDs (i.e., within 60 days). Information about Pre-RFD submissions (including the timeliness of OCP responses) is provided in the section below titled "Pre-RFD Workload Performance."

[10] Over the reported 5-year time frame, a 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 "Pre-RFD Workload Performance" for more information.

OCP received 50 RFD submissions in FY 2019 and carried over three RFD submissions that were undergoing review at the end of FY 2018. Of the 53 total submissions that were reviewed in FY 2019, decisions were issued for 13 submissions (25 percent), 35 submissions were found to have insufficient information for filing (66 percent), 3 submissions were pending at the end of FY 2019 (6 percent)[11] and 2 submissions were withdrawn by the sponsor prior to filing (4 percent).[12] OCP also issued one response to a Request for Reconsideration of an RFD decision by the 15-day review period, as specified by the regulations.

[11] These three submissions were undergoing review at the end of FY 2019 and were carried over to FY 2020.
[12] All percent values have been rounded to the nearest number for this entire report.

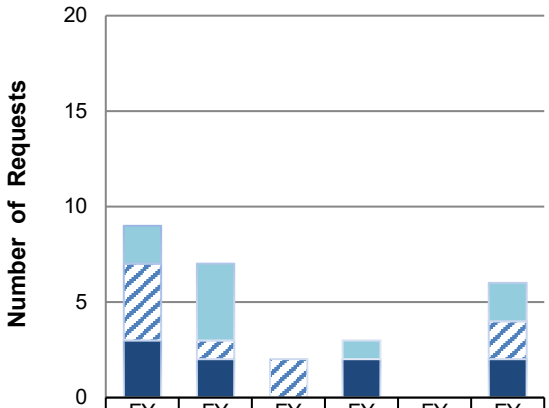
Table 2. Combination Product Determinations.



	FY 14	FY 15	FY 16	FY 17	FY 18	FY 19
Total	8	2	2	5	8	7
CBER	1	0	0	0	1	1
CDER	5	1	1	4	6	4
CDRH	2	1	1	1	1	2

As shown in Table 2, the total number of RFD combination product classifications and assignments issued in FY 2019 decreased by one compared to FY 2018.

Table 3. Non-Combination Product Determinations.



	FY 14	FY 15	FY 16	FY 17	FY 18	FY 19
Total	9	7	2	3	0	6
CBER	2	4	0	1	0	2
CDER	4	1	2	0	0	2
CDRH	3	2	0	2	0	2

As shown in Table 3, the total number of RFD non-combination product classifications and assignments issued in FY 2019 increased by six compared to FY 2018.

In FY 2019, the 13 RFD determinations were all issued by the statutorily mandated 60-day deadline. The average RFD review time was 57 days, with a median review time of 57 days. Tables 4 and 5 provide timeliness data by the product type of the issued RFD decision.

Table 4. Timeliness of Combination Product Determinations.

Determination	Product Assignments Issued*	Percent On Time*
Drug-Device	4	100%
Drug-Biologic	1	NA
Device-Biologic	2	100%
Drug-Device-Biologic	0	NA
Total	**7**	**100%**

* Does not include Request for Reconsideration responses, which are issued within the 15-day time frame provided by 21 CFR 3.8. One Request for Reconsideration was submitted for a combination product in FY 2019.

Table 5. Timeliness of Non-Combination Product Determinations.

Determination	Product Assignments Issued*	Percent On Time*
Drug	2	100%
Biologic	2	100%
Device	2	100%
Total	**6**	**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 2019.

Pre-RFD Workload Performance

In addition to handling RFDs, OCP provided preliminary feedback in response to Pre-RFD submissions for product classification and Center assignment (i.e., Pre-RFD assessments). The Pre-RFD process can offer more flexibility than the RFD process, for example, the Pre-RFD process allows for more discussions (e.g., teleconferences) between FDA and a sponsor if questions arise during the review. In Table 6, OCP's Pre-RFD submission review workloads from FY 2017 to FY 2019 are provided. FY 2019 is the third full year of the "formalized" Pre-RFD program.[13]

Table 6. OCP's Pre-RFD Workloads from FY 2017 to FY 2019.

Pre-RFD Assessments	FY 17	FY 18	FY 19
Combination Product Assessments	44	48	51
Non-Combination Product Assessments	34	28	29
Unclassified Assessments*	NA	6	3
Total Pre-RFD Assessments	**78**	**82**	**83**

* Pre-RFD assessments may not result in a classification as a drug, device, biological product, or combination product, and/or a Center assignment. For instance, products that fall under this unclassified category may meet the criteria for regulation solely under section 361 of the Public Health Service (PHS) Act and 21 CFR part 1271, or sponsor for these products may have pursued product assignment and not a classification.

Of the 83 total Pre-RFD assessments, 94 percent were issued by OCP's internally established 60-day goal date from OCP's receipt of sufficient information to provide the requested feedback.[14] In FY 2019, the 60-day review goal was missed for 5 submissions out of a total of 83. The average review time was 52 days, with a median review time of 58 days. The following tables (i.e., Tables 7 through 10) provide data on the Pre-RFD feedback for combination products and non-combination products based on the products' classification and the Center assignment.

[13] 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 have originated with the Centers and not with product sponsors). However, Pre-RFDs and Center requested consultations are two different OCP activities. Therefore, these two different data groups have been independently reported since FY 2017. Center requested consultations are discussed in the following section.

[14] 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).

Table 7. Number and Timing of Combination Product Pre-RFD Assessments by Center Assigment.

Classification	Pre-RFDs Issued	Percent Issued in 60 Days
Drug-Device	37	95%
Drug-Biologic	1	100%
Device-Biologic	8	88%
Drug-Device-Biologic	5	100%
Total	**51**	**94%**

Table 8. Number and Timing of Combination Product Pre-RFD Assessments by Center Assignment.

Center Assignment	Pre-RFDs Issued	Percent Issued in 60 Days
CDER	37	95%
CBER	6	83%
CDRH	8	100%
Total	**51**	**94%**

Table 9. Number and Timing of Non-Combination Product Pre-RFD Assessments.

Classification	Assignments Issued	Percent Issued in 60 Days
Drug	17	94%
Biologic	3	67%
Device	9	100%
Total	**29**	**93%**

Table 10. Number and Timing of Non-Combination Product Pre-RFD Assessments by Center Assignment.

Center Assignment	Pre-RFDs Issued	Percent Issued in 60 Days
CDER	17	94%
CBER	3	67%
CDRH	9	100%
Total	**29**	**93%**

OCP's Performance on Internal Center- or Office-Requested Product Classifications and Center Assignment Consultations

In addition to handling RFDs and Pre-RFDs submitted by industry/sponsors, OCP provides classification and Center-assignment feedback for combination and non-combination products in response to requests from Centers (i.e., Center-Assignment Consultations (CCA Consults)) and other offices. For instance, Centers may contact OCP for assistance in determining if the combination 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 Pre-RFD/RFD. The number of CCA Consults provided by OCP, which identified an assigned Center is presented in Table 11 below.

Table 11. Number of CCA Consults by Center from FY 2017 to FY 2019.

Center Assignment	FY 17	FY 18	FY 19
CDER	29	31	51
CBER	3	3	4
CDRH	16	14	14
Unassigned*	0	2	4
Total	**48**	**50**	**73**

*The term "unassigned" indicates that a determination/assessment of Center assignment was not made. This may be the case, for example, if the question before OCP concerns solely product classification.

Table 12 reports on OCP's activities that do not fall within the classification and assignment activities reported above, such as responding to questions about process (e.g., how to prepare an RFD or Pre-RFD) and providing feedback to sponsors regarding the design of studies (e.g., on adequacy to evaluate the PMOA). This category also includes responses to individual email queries and meetings and teleconferences that OCP holds with sponsors, which may lead to RFDs/Pre-RFDs or obviate the need for them.

Table 12. Additional Number of OCP's Product Classification and Assignment Activities from FY 2017 to FY 2019.

	FY 17	FY 18	FY 19
Jurisdiction/Classification Issues	528	529	463

OCP's FY 2019 Accomplishments

Table 13 below highlights OCP's accomplishments for classification and Center assignment for FY 2019.

Table 13. Specific FY 2019 Accomplishments by OCP.

Type of Activity	FY 2019 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 continued to: • Chair a working group composed of staff from CDER, CDRH, CBER, and the Office of the Chief Counsel (OCC) to clarify interpretive standards, and to address the classification and assignment for challenging categories of products • Pursue and support related policy initiatives, including clarifying standards for cross-labeled combination product status and clarifying the regulatory status of software used with a drug or biological product.
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 assignment issues before FDA.
Developing Part 21 CFR Part 3 regulations	OCP continued to lead efforts to finalize a rule to amend Part 3 for clarity and consistency with more recent legislative and policy developments.

Combination Product Premarket Review

OCP is responsible for ensuring the timely, effective, and aligned premarket review of combination products. This includes overseeing the timeliness of reviews, the alignment of feedback to sponsors, and the coordination of reviews in which more than one Center needs to participate.

In 2002, FDA established procedures for CBER, CDER, and CDRH staff to follow when requesting, receiving, handling, processing, and tracking inter-Center consults. These procedures were formally incorporated into the FDA Staff Manual Guide (SMG) 4101 (titled "Inter-Center Consult Request Process"). The SMG was significantly updated in June 2018 to reflect efforts to improve inter-Center coordination for combination products and enhance the timeliness and consistency of inter-Center reviews.

Consistent with OCP's mandates under the Cures Act, FDA continued its efforts to improve the inter-Center consult process for combination products in FY 2019, including a significant update to the information technology (IT) system. In addition, OCP continued to (1) enhance its monitoring of quantitative metrics on inter-Center consults and (2) solicit qualitative input, including feedback from users via focus groups and other forums. These efforts have been used to identify opportunities for improvements in the process, IT system, staffing utilization, and resources available to staff. Concurrent with these activities, under the Prescription Drug User Fee Act Reauthorization (now PDUFA VI) commitments, FDA initiated an independent third-party assessment of regulatory activities for combination products, including premarket reviews. A final report from this assessment is due to be issued in FY 2020 and will provide further input regarding best practices to broadly improve the inter-Center consult process and premarket review activities for combination products.

Number and Types of Combination Products Submitted for Premarket Review

FDA is required to report the number and types of combination products submitted for review. The following items explain FDA's performance data that will be presented in this subsection.

- Data on the number and types of combination products submitted for review in FY 2019 by CBER, CDER, and CDRH (includes submissions filed or received in FY 2019), as well as the timeliness of these reviews.
- When reporting timeliness in days for the review for CBER-led or CDER-led combination products, the PDUFA VI goals were referenced for priority and standard new drug applications (NDAs) and applicable biologics license applications (BLAs), the Generic Drug User Fee Amendments (now GDUFA II) goals were referenced for the FY 2019 goals for abbreviated new drug applications (ANDAs), and the Biosimilar User Fee Amendments (now BsUFA II) goals were referenced for the FY 2019 goals for biosimilar BLAs. For CBER-led or CDRH-led combination products, Medical Device User Fee Amendments (now MDUFA IV) goals were referenced for expedited and original premarket approval applications (PMAs), premarket notifications (510(k)s), De Novos, and device BLAs.

- Some product review goals, such as for NDAs, are defined by the number of months given to review the product. 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).
- The median review times were based on FDA's first-cycle review performance for PDUFA VI goals. For MDUFA IV goals, the median review times were based on the total MDUFA IV decision review time. The actual review time was used when only one action was measured.

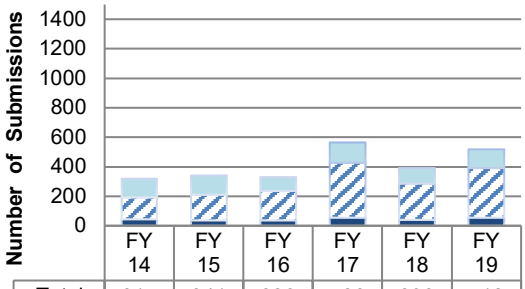
Requirement Workload Trends: FY 2014 to FY 2019

Table 14. FY 2014 to FY 2019 Submission Review Workloads.

Submission/Request	FY 14	FY 15	FY 16	FY 17	FY 18	FY 19
Total Combination Products (by Center) Submitted for Review	317	341	330	566	390	518

As shown in Table 14, the total number of combination products submitted for review increased from 317 original applications in FY 2014 to 518 original applications in FY 2019. As reflected in Table 15, of all combination product submissions, 65 percent were received by CDER, 25 percent were received by CDRH, and 10 percent were received by CBER.

Table 15. Combination Product Application Submissions by Center.



	FY 14	FY 15	FY 16	FY 17	FY 18	FY 19
Total	317	341	330	566	390	518
CDRH	126	129	95	138	102	126
CDER	147	175	199	375	246	339
CBER	44	37	36	53	42	53

Table 16 presents the 518 original applications for combination products received in FY 2019, broken down by the identified ten application types and by the product's initial classification into one of nine categories of combination products.[15] The same table reflecting applications received in FY 2018 is updated in Appendix A to reflect corrections and actions as of September 30, 2019. The majority of the applications received in FY 2019 were original investigational new drugs (INDs) (51 percent), followed by 510(k)s (17 percent). Also, the most common combination product category was the pre-filled drug delivery device/system (20 percent).

Table 16. Workload by Combination Product Category Number.

Application Type	1	2	3	4	5	6	7	8	9	Totals
Original NDAs	16	16	0	0	0	0	0	0	0	**32**
Original BLAs	2	0	4	0	0	2	2	0	0	**10**
Original PMAs	0	0	0	4	0	0	1	0	0	**5**
Original 510(k)s	18	0	0	63	1	0	8	0	0	**90**
Original INDs	20	32	27	1	12	54	11	87	19	**263**
Original Investigational Device Exemptions (IDEs)	3	0	0	14	1	0	4	5	3	**30**
Original Humanitarian Device Exemptions (HDEs)	0	0	0	0	0	0	0	0	0	**0**
Original ANDAs	27	55	0	0	0	0	0	0	0	**82**
Biosimilar BLAs	0	0	5	0	0	0	0	0	0	**5**
De Novos	0	0	0	1	0	0	0	0	0	**1**
Totals	**86**	**103**	**36**	**83**	**14**	**56**	**26**	**92**	**22**	**518**

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

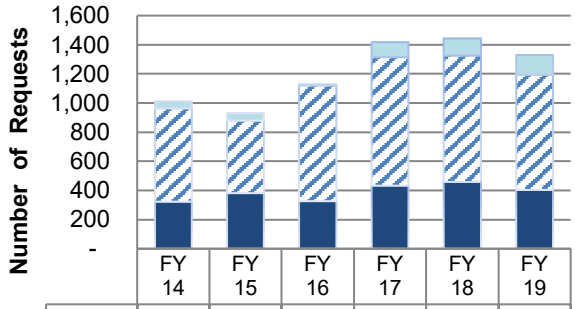
[15] The classifications are presented as initial because adjustments are made to these numbers for each fiscal year to reflect corrections and subsequent actions that may inform the classification status, such as the ultimate status of products initially placed in category 8 (for certain possible combination products).

Inter-Center Consult Requests

This section reports on the number of inter-Center consults for combination products, a related but distinct topic from the number of submissions for combination products. There can, for example, be multiple consults for a single combination product submission, or a submission may not warrant a consult because relevant expertise resides in the lead Center and consultation is not otherwise needed to ensure a consistency of review standards. Combination product consults to CDER from other Centers are most often for expertise related to chemistry, manufacturing, and controls; biopharmaceutics; or clinical review expertise. Combination product consults to CDRH from other Centers are most often for review expertise related to the technical (e.g., biocompatibility) and engineering/performance review of delivery devices or for assessments of facilities for premarket applications; other consult topics include human factors/user interfaces, and software.[16]

As shown in Table 17, in FY 2019, there were 1,328 inter-Center consults, which was 12 percent higher than the average for the last 5 years but a decrease of 8 percent compared to FY 2018.

Table 17. Inter-Center Consultation Requests by Lead/Reviewing Center.



	FY 14	FY 15	FY 16	FY 17	FY 18	FY 19
Total	1,013	932	1,130	1,419	1,445	1,328
CBER	48	53	9	105	118	133
CDER	643	499	793	881	867	792
CDRH	322	380	328	433	460	403

[16] Of note, there are other inter-Center consults that may not directly involve combination products, such as regarding the use of companion diagnostics with drug or biological products that do not comprise a combination product, investigational studies that involve another Center's products or expertise, and requests for clinical expertise that may not be available in a particular Center. Furthermore, cross-Center collaboration also occurs through additional pathways (e.g., the Medical Oncology Review and Evaluation team of FDA's Oncology Center of Excellence). These consults are not captured in the counts below but are often conducted under the same process as outlined in SMG 4101.

In Table 18, the total number of inter-Center consults in FY 2019 is compared to the previous 5-year averages.

Table 18. FY 2014 to FY 2019 Inter-Center Consult Workloads.

Submission/Request	FY 14	FY 15	FY 16	FY 17	FY 18	FY 19	FY 14 to FY 18 5-Year Average	FY 19 Compared to 5-Year Average
Total Inter-Center Consult Requests	1,013	932	1,130	1,419	1,445	1,328	1,188	+ 12%

In Table 19, the number of inter-Center consult requests during FY 2019 is broken down by the lead Center (i.e., the Center requesting the consult) and the consulted Center (i.e., the reviewing Center).

Table 19. Number of Premarket Review Inter-Center Consults for Combination Products by Lead and Consulted Center.

Lead Center	Consulted Center			
	CBER	CDER	CDRH	Number of Consults
CBER	--	36	97	133
CDER	29	--	763	792
CDRH	7	396	--	403
Total	**36**	**432**	**860**	**1,328**

In Table 20, the number of inter-Center consults is broken down by application type at each Center.

Table 20. Number of Premarket Review Inter-Center Consults by Application Type and Lead Center.*

Application Type	Lead Center			
	CBER	CDER	CDRH	Number of Consults
ANDA	--	124	--	124
BLA	7	68	--	75
IND / Pre-IND	103	409	--	512
NDA	3	186	--	189
510(k)	7	--	11	18
De Novo	--	--	15	15
IDE	4	--	77	81
PMA	1	--	93	94
Pre-Submission	8	--	195	203
Other		5	12	17
Total	**133**	**792**	**403**	**1,328**

* Inter-Center consult counts include consults for supplements, amendments, etc., not just for original submissions.

Timeliness in Days of the Reviews of Combination Products

FDA is required to report the timeliness of reviews for combination products. Table 21 summarizes the review types and applicable review performance targets for original NDAs, ANDAs, PDUFA BLAs, BsUFA BLAs, PMAs, De Novos, and 510(k)s. PDUFA VI, GDUFA II, BsUFA II, and MDUFA IV 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 have an action within a specified time frame. Performance goals apply only to 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 IV performance goals, refer to https://www.fda.gov/media/102699/download.
- For PDUFA VI performance goals, refer to https://www.fda.gov/media/99140/download.
- For GDUFA II performance goals, refer to https://www.fda.gov/media/101052/download.
- For BsUFA II performance goals, refer to https://www.fda.gov/media/100573/download.

Table 21. Performance Goals for Original Applications.[†]

User Fee Program	Original Application Type	Review Type	Review Within
PDUFA VI	NDAs	Priority	6 Months
PDUFA VI	NDAs	Standard	10 Months
PDUFA VI	BLAs	Priority	6 Months
PDUFA VI	BLAs	Standard	10 Months
MDUFA IV	Expedited and Original PMAs	Standard with No Advisory Committee Input	180 Days
MDUFA IV	Expedited and Original PMAs	Standard with Advisory Committee Input	320 Days
MDUFA IV	510(k)s	Standard	90 Days
MDUFA IV	BLAs	Priority	6 Months
MDUFA IV	BLAs	Standard	10 Months
BsUFA II	Biosimilar BLAs	Standard	10 Months
GDUFA II	ANDAs	Standard	10 Months
GDUFA II	ANDAs	Priority	10 Months
GDUFA II	ANDAs	Priority with Pre-Submission Facility Correspondence	8 Months
MDUFA IV	De Novos	Standard	150 Days

[†] The timelines for new medical entities and BLAs that fall under PDUFA VI'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's 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 in which FDA received them, regardless of when FDA acted on or approved the submissions. The following subsection, entitled "FY 2018 and FY 2019 Review Performance", updates FDA's final review performance on the FY 2018 combination product submissions and presents FDA's preliminary review performance on the FY 2019 combination product submissions through September 30, 2019.

FY 2018 and FY 2019 Review Performance

Table 22 shows the final FY 2018 review goal performance.

Table 22. Final FY 2018 Review Goal Performance.

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	183	12 to 333
NDAs	Standard	10 Months	9	304	301 to 455
BLAs	Priority	6 Months	2	288.5	244 to 333
BLAs	Standard	10 Months	3	334	303 to 365
Expedited and Original PMAs	Standard	180 or 320 Days†	3	178	158 to 266
510(k)s	Standard	90 Days	61	86	29 to 94
Biosimilar BLAs	Standard	10 Months	1	361	361
ANDAs	Standard	10 Months	46	299.5	227 to 348
ANDAs	Priority	8 Months	2	271.5	248 to 295
ANDAs	Priority with Pre-Submission Facility Correspondence	8 Months	1	243	243
De Novos	Standard	150 Days	2	118	84 to 151

† This includes a review within 180 days for decisions without advisory committee input or a review within 320 days for decisions with advisory committee input, respectively.

Table 23 shows preliminary FY 2019 review goal performance through September 30, 2019.

Table 23. Preliminary FY 2019 Review Goal Performance.

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	6	209	94 to 273
NDAs	Standard	10 Months	26	304	301 to 393
BLAs	Priority	6 Months	2	134.5	113 to 156
BLAs	Standard	10 Months	8	298	285 to 298
Expedited and Original PMAs	Standard	180 or 320 Days†	5	177.5	175 to 180
510(k)s	Standard	90 Days	90	87	21 to 90
Biosimilar BLAs	Standard	10 Months	4	364	364
ANDAs	Standard	10 Months	82	297	224 to 302
ANDAs	Priority	8 Months	2	286.5	280 to 293
ANDAs	Priority with Pre-Submission Facility Correspondence	8 Months	1	242	242
De Novos	Standard	150 Days	1	217	217

† This includes a review within 180 days for decisions without advisory committee input or a review within 320 days for decisions with advisory committee input, respectively.

Premarket Review Facilitation/Oversight

OCP continues to facilitate the premarket review of combination products that raise complex regulatory issues. OCP fosters early interactions between industry and FDA to help clearly delineate the regulatory pathways for the development of combination products and expeditiously review the 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 (1) on the appropriate use and interpretation of combination product categorization for premarket submissions and (2) in determining the correct combination product categories for data reporting purposes. Finally, OCP leads or participates in meetings and discussions to ensure efficient, effective communication between sponsors and FDA review staff and to align data expectations among Centers and for products raising similar regulatory questions. The number of OCP's product-specific documented premarket review actions from FY 2014 to FY 2019 are presented in Table 24.

Table 24. Number of OCP's Documented Premarket Activities from FY 2014 to FY 2019.

	FY 14	FY 15	FY 16	FY 17	FY 18	FY 19	FY 14 to FY 18 5-Year Average	FY 19 Compared to 5-Year Average
Premarket Review Activities	402	225	266	525	321	144	348	-59%

In FY 2019, as shown in Table 24, OCP received 144 requests for product-specific assistance, the responses to which contributed to ensuring the timely, effective, and aligned review of combination products. This number of requests represents a 59 percent decrease compared to the FY 2014 to FY 2018 5-year average.[17] Notably, OCP addressed issues including the following:

- Novel drug and biological products combined with new technological delivery systems (e.g., emergency use products and complex generic drug-device combination products);
- Alignment of preclinical and biocompatibility data requests;
- Review of combination products for rare disease populations;
- Alignment of potential clinical hold review assessments;
- Accuracy, consistency, and clarity of the labeling of separately distributed constituent parts;
- Alignment of warning letter considerations with ongoing developmental considerations for a platform constituent part of several combination products;
- Ongoing development considerations of combination products that incorporate mobile communication technologies or digital health innovations.

In addition, OCP oversees the inter-Center consults by facilitating a coordination among review Centers (i.e., to ensure that reviews of premarket applications are completed in a timely manner and meet applicable user fee timelines). Specifically, OCP tracks and monitors all ongoing

[17] Please note that the reported decrease in such OCP premarket activities coincided with the implementation of the Inter-Center Consult Report, which was launched in FY 2018 and FY 2019, which enhanced training and resources for Centers' staff.

inter-Center consult requests; clarifies internal operating procedures, roles, and responsibilities; identifies consulting divisions and contacts; clarifies due dates and completion statuses; facilitates access to review documents; and works to resolve other barriers to the timely completion of consults. OCP also periodically reviews inter-Center consult data requests and conducts additional assessments, as needed, to ensure that the inter-Center consult request process supports the timely, consistent, and effective review of combination products. Additionally, OCP receives and responds to external requests for OCP assistance in resolving Center timeliness (i.e., communications and/or clarification of product specific review findings). Finally, OCP facilitates the resolution of master file review communication uncertainties.

OCP provides facilitation or assistance to the Centers and industry regarding regulatory and scientific issues relating to specific combination products or to specific categories of combination products. Detailed accomplishments during FY 2019 are presented in Table 25.

Table 25. OCP's Provision of Significant Premarket Review Facilitation or Assistance During FY 2019.

Type of Activity	FY 2019 Accomplishments
Providing Significant Premarket Review Facilitation or Assistance	Provided significant facilitation or assistance with respect to the following categories of products and other premarket regulatory issues: • Novel drug-device cancer therapies; • Injector delivery systems (e.g., intrathecal and on-body-wearable pump infusion systems); • Medical imaging drugs with photodynamic device activating and imaging systems; • Facilitation of premarket current good manufacturing practice (CGMP) assessments; • Application of 21 CFR part 4 to premarket submissions under review; • Inter-Center review of manufacturing process compliance; • Inter-Center safety evaluator processes; • Clarification of the IND human factors protocol submission process and the review of these study results; • Implications of the Drug Supply Chain Security Act on a CDRH-led combination product; • Unique device identifiers and standardized numerical identification; • Alignment of IND and IDE review requirements for combination products; • Considerations on the Agency's requirement of two marketing applications for a specific combination product.

Combination Product Postmarket Activities

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

OCP meets the requirement to ensure this consistency and appropriateness by undertaking a variety of compliance-related and postmarket activities to help ensure the safety and quality of combination products. These compliance-related and postmarket activities include leading the Agency's efforts to develop and publish regulations and issue guidances regarding postmarket safety reporting (PMSR) and CGMPs for combination products (as discussed more fully in the "Policy Activities and Accomplishments" section below), coordinating and overseeing FDA's 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. For example, OCP provides support to FDA's field investigators on CGMP facility inspection issues and on the seizure of products at ports of entry to stop adulterated/misbranded products from entering the United States, assists the Agency in responding to product defect issues, and provides assistance on enforcement issues to other Agency components, including on the development of compliance and enforcement action communications such as warning letters. In addition, OCP works with other Agency components to develop and present trainings, procedures, IT updates, and other tools to enhance the efficiency and consistency of postmarket regulatory activities.

OCP's FY 2019 accomplishments related to the consistency and appropriateness of postmarket regulations are included in Table 26 (see also the "Policy Activities and Accomplishments" section below).

Table 26. Documented Product-Specific Postmarket Regulatory Activities from FY 2014 to FY 2019.

	FY 14	FY 15	FY 16	FY 17	FY 18	FY 19	FY 14 to FY 18 5-Year Average	FY 19 Compared to 5-Year Average
Postmarket Regulatory Activities	110	71	50	74	86	62	78	-21%

OCP engaged in 62 product-specific, postmarket-related matters involving issues such as the application of CGMPs and quality system regulations for inspections of combination products, the appropriate mechanisms and responsibilities for reporting adverse events, and the requirements for registration and listing. This number represents a 21 percent decrease in the number of such activities as compared to the prior 5-year average. In addition, at the request of the Centers, OCP facilitated or led working groups to assess safety signal evaluations to determine the Agency's response to the safety issue.

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

- Enhancing the efficiency and consistency of coordination among the Agency's components in support of CGMP inspectional and compliance policies and practices;
- Clarifying stakeholders' and FDA's understanding of the PMSR requirements (see also the discussion of a final guidance under the "Policy Activities and Accomplishments" section below);
- Facilitating the implementation of the PMSR requirements through updates to systems and instructions to clarify how to make compliant reports.

Effective Resolutions of Review Disputes

When OCP receives a formal request to resolve a dispute regarding the timeliness of the premarket review of a combination product, OCP is required to do so. OCP also facilitates communications between sponsors and FDA review staff to identify, clarify, and resolve specific concerns associated with the review's timeliness. This facilitation helps prevent the need for more formal dispute resolutions.

In addition to sponsor requests for addressing premarket review timeliness issues, OCP may receive requests for dispute resolution and/or mediation for other regulatory issues (e.g., inter-Center review dispute resolution or requests by product sponsors for assistance either in understanding a review division's intent regarding issued decisions or in resolving differences of view regarding regulatory requirements).

Percentage of Combination Products Reviewed 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. FDA received no formal requests for dispute resolution in FY 2019. Therefore, the percentage is zero of the total combination product submissions (i.e., based on the total number of combination product submissions reported in the "Combination Product Premarket Review" section of this report). The "Premarket Review Facilitation/Oversight" data in this report provides examples of informal facilitation and resolution of issues related to premarket review.

Policy Activities and Accomplishments

Regulatory Initiatives

OCP's activities include leading and assisting with policy initiatives important to the regulation of combination products. Examples of such activities pursued in FY 2019 are discussed below (and included in the following tables).

Supporting Legislative Initiatives

OCP participated in the development of FDA's positions in response to congressional inquiries. Furthermore, OCP continued its efforts, in coordination with the medical product Centers, to implement section 3038 of the Cures Act regarding combination products. Activities in this regard included the following: the issuance of new rules and guidance documents and the enhancement of standard operating procedures (SOPs), IT improvements, staff training, and outreach to stakeholders. OCP also participated in the implementation of section 706 of the FDA Reauthorization Act of 2017 ("Fostering Innovation in Medical Imaging") and was involved in the implementation of PDUFA VI activities related to combination products (e.g., developing the bridging and human factors guidance documents).

Streamlining Regulation

OCP continued its work on amending FDA's jurisdictional regulations in 21 CFR part 3, considering comments received on the proposed rule,[18] to update and clarify them in light of legislative and other policy developments.

Providing Clarifying Guidance

OCP collaborated with the medical product Centers to develop and publish regulations, guidance documents, notices, safety communications, and internal procedures, including the following:

- Proposed rule on De Novo classification;[19]
- Final guidance on PMSR for combination products and compliance enforcement;[20]
- Final guidance on requests for feedback and meetings under the Q-Submission Program[21]
- Final guidance on devices used with regenerative medicine therapies;[22]

[18] Available at https://www.govinfo.gov/content/pkg/FR-2019-05-15/pdf/2019-10321.pdf.
[19] Available at https://www.federalregister.gov/documents/2018/12/07/2018-26378/medical-device-de-novo-classification-process
[20] Available at https://www.fda.gov/media/111788/download, https://www.fda.gov/media/95120/download
[21] Available at https://www.fda.gov/media/114034/download
[22] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-devices-used-regenerative-medicine-advanced-therapies

- Final guidance on the "least burdensome" statutory provisions;[23]
- Final guidance on the package type and labeling for injectable medical products;[24]
- Draft guidance on safer technologies;[25]
- Draft guidance on clinical decision support software;[26]
- Draft guidance on instructions for use labeling content and format;[27]
- Draft guidance on premarket pathway principles for combination products;[28]
- Draft guidance on drug master files for drug-led combination products including electronics or software;[29]
- Draft guidance on peripheral percutaneous transluminal angioplasty and specialty catheters - 510(k)- submissions;[30]
- *Federal Register* request for comments on prescription drug-use-related software;[31]
- *Federal Register* notice regarding FDA's intent to consider the classification of hyaluronic products for the treatment of osteoarthritic pain;[32]
- *Federal Register* notice for public meetings on the instructions for the electronic reporting of adverse events using the E2B(R3) standard;[33]
- FDA Safety Communication on using caution with implanted pumps for the intrathecal administration of medicines for pain management;[34]
- FDA Safety Communication warning against the use of teething necklaces, bracelets, or other jewelry marketed for relieving teething pain or providing sensory stimulation;[35]
- SMG 4104 on inter-Center consults for human factors reviews.[36]

[23] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles
[24] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/selection-appropriate-package-type-terms-and-recommendations-labeling-injectable-medical-products
[25] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safer-technologies-program-medical-devices
[26]Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-decision-support-software
[27] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/instructions-use-patient-labeling-human-prescription-drug-and-biological-products-and-drug-device
[28] Available at https://www.fda.gov/media/119958/download
[29] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/type-v-dmfs-cder-led-combination-products-using-device-constituent-parts-electronics-or-software
[30] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/peripheral-percutaneous-transluminal-angioplasty-pta-and-specialty-catheters-premarket-notification
[31] Available at https://www.federalregister.gov/documents/2018/11/20/2018-25206/prescription-drug-use-related-software-establishment-of-a-public-docket-request-for-comments
[32] Available at https://www.federalregister.gov/documents/2018/12/18/2018-27351/intent-to-consider-the-appropriate-classification-of-hyaluronic-acid-intra-articular-products
[33] Available at https://www.govinfo.gov/content/pkg/FR-2019-03-14/pdf/2019-04730.pdf
[34] Available at https://www.fda.gov/medical-devices/safety-communications/use-caution-implanted-pumps-intrathecal-administration-medicines-pain-management-fda-safety
[35] Available at https://www.fda.gov/medical-devices/safety-communications/fda-warns-against-use-teething-necklaces-bracelets-and-other-jewelry-marketed-relieving-teething
[36] Available at https://www.fda.gov/media/120204/download

In addition, OCP led ongoing cross-Center activities to revise and finalize the published draft guidance for "Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development".

Other Policy-Related Activities

Additional policy-related activities included the following:

- Enhancement of procedures and mechanisms for monitoring and enhancing the combination products premarket and postmarket regulatory activities, consistent with section 3038 of the 21st Century Cures Act;
- Continued evaluation and updating of procedural and IT systems to enable the implementation of the final PMSR rule for combination products;
- Participation in the issuance of SMG 4104 on the inter-Center consults for the review of human factors information.[37]

Tables 27 through 29 identify other policy initiatives in which OCP participated, relating to jurisdiction, premarket review, and postmarket regulation, presented by activity type.

Table 27. Additional Jurisdictional Regulatory Initiatives.

Type of Activity	FY 2019 Accomplishments
Developing regulations and guidance	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 PHS Act.[38]
Participating in other inter-Center and Agency-wide working groups to clarify issues related to product jurisdiction	OCP jurisdiction-related activities included the following: • Enhancement of the efficiency and transparency of the Pre-RFD program; • Classification-related issues for e-cigarettes and other products that include tobacco.

[37] Available at https://www.fda.gov/media/120204/download
[38] Available at https://www.govinfo.gov/content/pkg/FR-2019-12-12/pdf/2019-26840.pdf

Table 28. Additional Premarket Review Regulatory Initiatives.

Type of Activity	FY 2019 Accomplishments
Developing regulations and guidance	• OCP continued to chair a cross-Center working group to finalize a guidance on human factors studies for combination products. • OCP continued to chair a cross-Center working group to develop a draft guidance for technical aspects of intravaginal ring drug-delivery combination products. • OCP chaired a cross-Center working group to develop a guidance for the technical considerations for demonstrating reliability of combination product emergency-use injectors. • OCP led the development of a Cures Act-mandated guidance on presubmissions for combination product and combination product agreement meetings. OCP participated in the development of the following: • Rulemaking on De Novo classification; • Guidance on bridging for drug and biologic-led combination products; • Guidance on pre-submission facility inspections for generic drugs;[39] • Guidance on metered dose inhalers and dry powder inhalers;[40] • Comments for citizen petition responses for specific types of generic combination products; • Technical considerations for the visual inspection of particulates in injectable solutions; • Comments on International Organization for Standardization standards development for certain syringes.
Assessing 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.
Participating in other inter-Center and Agency-wide working groups to clarify issues related to the combined use of medical 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; • Non-prescription drug availability; • The Agency's thinking on the regulation of software as drug labeling; • Agency-wide working groups such as FDA's Task Force on Antimicrobial Resistance.

[39] Available at https://www.fda.gov/media/105794/download
[40] Available at https://www.fda.gov/media/70851/download

Type of Activity	FY 2019 Accomplishments
Coordinating with other Centers	OCP led or participated in working groups with the Centers regarding the monitoring and continuous improvement of the inter-Center consult process, including IT development and enhancement. OCP developed agreements and SOPs regarding when and how Centers consult with each other and, when needed, OCP for combination product issues.

Table 29. Additional Postmarket Review Regulatory Initiatives.

Type of Activity	FY 2019 Accomplishments
Participating 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. Work focused on the development of a final guidance regarding the final rule and efforts to implement the rule, including internal training and development of internal SOPs. • 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 programs with respect to combination products, including Unique Device Identifier, numeric drug coding, and serialized numeric identifiers. • OCP continued to co-chair a committee on combination products of the Association for the Advancement of Medical Instrumentation that continued work on a technical information report on risk management for combination products.

Additional Activities and Accomplishments

Information Technology

OCP continued to coordinate and participate in cross-cutting IT initiatives to enhance the 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 launched a new technology platform to facilitate cross-Center collaboration for the review of combination products. In light of the final rule on PMSR for combination products, OCP also initiated a project to integrate, to the extent feasible, data on combination products from different data sources such as premarket systems, registration and listing, and adverse event reporting systems from all three medical product Centers into a single point of reference to enhance the efficiency and consistency of postmarket safety activities. Finally, OCP began work to develop a new electronic system for Pre-RFD and RFDs.

External Outreach

OCP conducted outreach on FDA's assignment and regulation of combination products by meeting and otherwise engaging with trade associations and coalitions (e.g., Combination Products Coalition, Advanced Medical Technology Association, Association for Advancement of Medical Instrumentation, The Pharmaceutical Research and Manufacturers of America, and the Biotechnology Innovation Organization representing the drug, device, biological product, and combination product industries, as well as by participating in industry conferences. Discussions and presentations focused on a wide range of topics, including emerging issues in combination product regulation, the role of OCP, policies and guidance documents under consideration, rulemakings, specific categories of combination products, particular regulatory issues, and stakeholder priorities for further action. Examples of OCP's FY 2019 outreach activities are included in the table below.

Table 30. Examples of FY 2019 Outreach Activities.

Type of Activity	FY 2019 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: • Drug Information Association (DIA) Pharmacovigilance and Risk Management (January 2019); • 2019 DIA Annual Conference on Combination Products; • Parenteral Drug Association/FDA Joint Regulatory Conference 2019; • DIA Annual Meeting 2019; • Institute of Electrical and Electronics Engineers conference - Microwave Theory and Techniques Twin Cities Workshop (December 13, 2018); • Xavier University Health Combination Products Summit (September 2019); • 2018 DIA Combination Products Conference (October 2018); • 2018 DIA Complex Drug-Device Generic Combination Products Conference (October 2018); • Medical Device Manufacturers Association 2019 FDA Forum;

Type of Activity	FY 2019 Accomplishments
	• 2019 Medtech Summit (Brussels via teleconference); • 2019 Food and Drug Law Institute Annual Conference.

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Appendix A: FY 2018 Updated Performance Detail

The table below reflects the 390 original applications classified into one of nine categories of combination products received in FY 2018.

Workload by Combination Product Category Number

Application Type	1	2	3	4	5	6	7	8	9	Totals
Original NDAs	1	11	0	0	0	0	1	0	0	**13**
Original BLAs	1	0	3	0	0	1	0	0	0	**5**
Original PMAs	0	0	0	2	1	0	0	0	0	**3**
Original 510(k)s	7	0	0	50	1	0	2	0	8	**68**
Original INDs	17	28	34	4	6	40	6	75	5	**215**
Original IDEs	6	0	0	15	3	0	4	3	6	**37**
Original HDEs	0	0	0	0	0	0	0	0	0	**0**
Original ANDAs	14	32	0	0	0	0	0	0	0	**46**
Biosimilar BLAs	0	0	1	0	0	0	0	0	0	**1**
De Novos	0	0	0	2	0	0	0	0	0	**2**
Totals	**46**	**71**	**38**	**73**	**11**	**41**	**13**	**78**	**19**	**390**

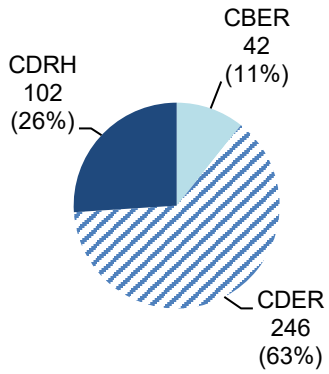
Combination Product Category Key:

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 2018 by Center lead, as of September 30, 2019.

Combination Product Applications (n = 390)



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 and Evaluation, 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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This report is available on FDA's home page at www.fda.gov and on OCP's home page at https://www.fda.gov/combination-products.