FY 2020

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 2020 annual performance report to Congress for the Office of Combination Products (OCP), an office in the U.S. Food and Drug Administration (FDA). This report includes data from the 17th full year since OCP was established, which was 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 be handled 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 its processes for assigning combination products to the appropriate lead Center and that Center's regulation. OCP facilitates interactions between industry and FDA to clearly delineate regulatory pathways; monitor and adjust processes to ensure a timely and effective, aligned premarket review; and help ensure consistent and appropriate postmarket regulation of combination products. In addition to handling combination products, OCP classifies and assigns products as drugs, devices, and biological products.

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

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

Janet Woodcock, M.D.
Acting Commissioner of 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 (1) the prompt assignment of combination products (drug-device, biologic-device, drug-biologic, or drug-device-biologic products) to FDA's Centers; (2) the timely, effective, and aligned premarket review of applications for these products; and (3) the consistent and appropriate postmarket regulation of combination products subject to the relevant statutory requirements to the extent permitted by law.

This annual performance report to Congress covers OCP's activities and accomplishments during fiscal year (FY) 2020 (i.e., October 1, 2019, to September 30, 2020). The following activities of OCP for FY 2020, of which the first three relate to a mandate listed above, as well as OCP's performance results for each activity, are highlighted in this report:

1. **Prompt Assignment of Combination Products.** In FY 2020, 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 two non-combination product RFD decisions, with every classification and/or assignment decision meeting the 60-day statutory decision time requirement. OCP also provided timely classification and jurisdictional feedback for 79 separate Pre-Request for Designation submissions.

2. **Timely and Effective Combination Product Premarket Review.** In FY 2020, OCP received 188 requests for product-specific premarket assistance, the responses to which contributed to ensuring OCP's timely, effective, and aligned review of combination products. 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, clarify regulatory standards, address challenging categories of products, update the premarket review process, and address developmental considerations for combination products.

    a. FDA received 559 original premarket applications for combination products in FY 2020. There were 1,146 inter-Center consulting reviews for combination products in FY 2020. Examples of combination product types can be found on the Combination Products website.[1]

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

3. **Consistent and Appropriate Postmarket Regulation**. In FY 2020, OCP provided clarification and support for 113 separate postmarket matters. OCP continued to chair FDA working groups to address current good manufacturing practices (CGMP) and postmarketing safety reporting (PMSR) requirements for combination products. Notably, OCP published a Compliance Program for CGMP facility inspections for combination products and conducted training and other activities in support of its implementation, including continued updates to facility tracking databases. In addition, OCP worked with other Agency components to enhance training, databases, and resources to support postmarket safety issue investigations and to support implementation of the 2016 PMSR rule.[2] 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 2020, OCP continued to implement section 3038 of the 21st Century Cures Act and to provide direction regarding complex policy and procedural questions for combination products, other separately distributed medical products intended for combined use, and the classification and assignment of medical products. The Combination Products Policy Council, chaired by OCP and consisting of senior leaders from all three human medical product Centers and the Office of Clinical Policy and Programs, continued to offer support for such OCP activities. OCP issued two draft guidances, one on how a combination product sponsor can obtain feedback from FDA on scientific and regulatory questions[3] and the other on technical considerations for demonstrating the reliability of emergency use injectors.[4] OCP also issued a *Federal Register* notice explaining that FDA intends not to pursue a potential approach to enable device sponsors to obtain marketing authorization for their products labeled for a new use with an approved, marketed drug.[5] Other topics addressed in FY 2020 included human factors, the inter-Center consult process, access to relevant postmarket information via a dashboard, the availability of premarket pathways for combination products, and regulatory considerations for cross-labeled combination products and other separately distributed medical products intended for combined use. OCP also continued to conduct external outreach activities through engagement with stakeholder organizations and through a variety of educational and informational presentations to national and international audiences. These activities were intended to foster greater efficiency, consistency, and transparency of the combination product development and premarket review processes by enhancing understanding of the complex regulatory and scientific issues that arise for combination products. These

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[2] 81 FR 92603 (Dec. 20, 2016). See the guidance for industry and Food and Drug Administration staff *Compliance Policy for Combination Product Postmarketing Safety Reporting* (April 2019), available at www.fda.gov/media/111795/download.

[3] Available at www.fda.gov/regulatory-information/search-fda-guidance-documents/requesting-fda-feedback-combination-products.

[4] Available at www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-demonstrating-reliability-emergency-use-injectors-submitted-under-bla-nda.

[5] Available at www.federalregister.gov/d/2020-09832.

activities were also intended to clarify how stakeholders can work with FDA to address these issues and enable FDA to understand and consider stakeholders' questions and concerns.

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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
ICH – International Council for Harmonisation
IDE – investigational device exemption
IND – investigational new drug application
ISO – International Organization for Standardization
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

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 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 like products to the extent permitted by law." In response, FDA established the Office of Combination Products (OCP) within the Office of the Commissioner. In addition, section 3038 of the 21st Century Cures Act (Cures Act) (enacted December 13, 2016) 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 website.[6]

Description of Combination Products

Title 21 of the Code of Federal Regulations (CFR) (section 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 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 (1) have the potential to provide enhanced therapeutic advantages compared to non-combination medical products (i.e., devices, drugs, and biological products) and (2) incorporate cutting-edge, novel technologies that hold great promise for advancing patient care. Combination products may incorporate, for example, advanced delivery systems and may include 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 lifecycle from decisions relating to product jurisdiction to duties relating to the premarket review and postmarket oversight of combination products.[7] 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).

Specifically, section 503(g)(8) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353 (g)(8)) requires OCP to:

(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

[7] Under the Prescription Drug User Fee Act Reauthorization of 2017 (PDUFA VI) commitments, FDA initiated an independent third-party assessment of FDA's regulatory activities for combination products, including premarket reviews. A final report from this assessment issued in August, 2020, which is available at (www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vi-assessment-combination-product-review-practices-pdufa-vi). The report found FDA's jurisdictional, inter-Center consult request and premarket review practices for combination products fundamentally sound but offered recommendations to improve FDA's efficiency, to enhance FDA's practices through "straightforward" and "minor" refinements to processes, and to address technological challenges. These recommendations aligned with ongoing Agency efforts to improve and enhance these practice areas, including efforts discussed in this FY 2020 Performance Report.

practices specific to the assignment of combination products.

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 U.S.C. 360bbb-2 and 21 CFR part 3, "Product Jurisdiction." RFDs may request (1) a classification of a particular product as a biological product, device, drug, or combination product, (2) a determination of the product's Center assignment, or (3) both. FDA's responses to RFDs, with respect to classifications and/or Center assignments, are binding determinations that may only be changed under the conditions specified in 21 U.S.C. 360bbb-2 and 21 CFR 3.9.

Performance Results Presented in This Report

This report presents OCP's fiscal year (FY) 2020 activities and accomplishments. These reportable measures address mandated functions of OCP. Specifically, this report presents information and data on OCP's activities related to the following:[8]

- 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 are as of September 30, 2020.

[8] 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 implementation of the Cures Act 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)). (RFD submissions are subject to a statutory 60-day deadline for FDA response.) OCP also provides responses to Pre-Request for Designation (Pre-RFD) requests for assistance regarding product classification and assignment.[9] In addition, OCP leads some and supports other Agency efforts to develop and publish regulations, issue guidances, and develop other public-facing documents regarding medical product classification and assignment (as discussed more fully in the "Policy Activities and Accomplishments" section below).

Requirement Workload Trends: FY 2015 to FY 2020

OCP received 58 RFD submissions in FY 2020. In addition, OCP reviewed three RFD submissions that were carried over at the end of FY 2019. Of the 61 total RFD submissions that were reviewed in FY 2020, nine submissions (15 percent[10]) had a decision issued, 46 submissions (75 percent) were found to have insufficient information for filing, four submissions (seven percent) were pending at the end of FY 2020,[11] and two submissions (three percent) were withdrawn by the sponsor prior to filing. Of the nine RFD determinations, seven were classified as combination products and two were classified as non-combination products.[12]

In Table 1, the total number of RFD determinations (i.e., classifications and assignments for both combination and non-combination products) in FY 2020 is compared to the previous 5 years.

[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." Tables 7-10 in this report show the percent of pre-RFD assessments issued within FDA's internal goal of 60 days.

[10] All percent values have been rounded to the nearest whole number for this entire report.

[11] These four submissions were undergoing review at the end of FY 2020 and were carried over to FY 2021.

[12] OCP did not receive any Requests for Reconsideration in FY 2020.

Table 1. RFD Determinations from FY 2015 to FY 2020.[13]

RFD Submissions	FY 15	FY 16	FY 17	FY 18	FY 19	FY 20
Total RFD Combination Product Classifications/ Assignments	2	2	5	8	7	7
Total RFD Non-Combination Product Classifications/ Assignments	7	2	3	0	6	2

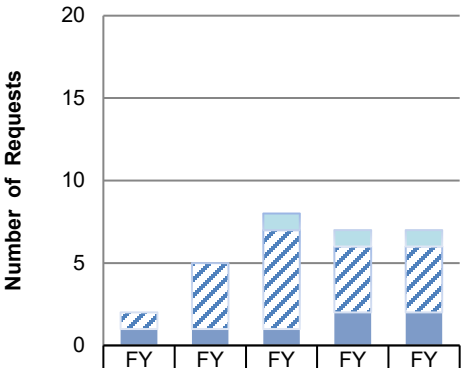
In FY 2020, the nine RFD determinations were all issued by the statutorily mandated 60-day deadline. The average RFD review time was 58.7 days, with a median review time of 59 days.

[13] 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.

As shown in Table 2, the total number of RFD combination product classifications and assignments issued in FY 2020 remained the same in FY 2019.

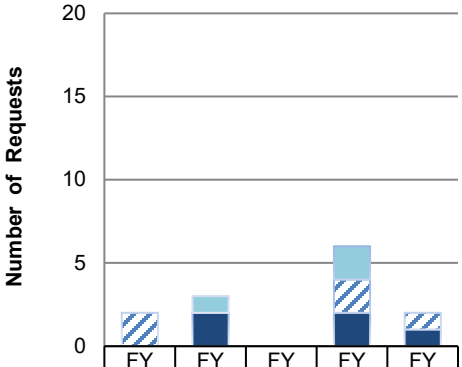
As shown in Table 3, the total number of RFD non-combination product classifications and assignments issued in FY 2020 decreased by four compared to FY 2019.

Table 2. Combination Product Determinations.



	FY 16	FY 17	FY 18	FY 19	FY 20
Total	2	5	8	7	7
CBER	0	0	1	1	1
CDER	1	4	6	4	4
CDRH	1	1	1	2	2

Table 3. Non-Combination Product Determinations.



	FY 16	FY 17	FY 18	FY 19	FY 20
Total	2	3	0	6	2
CBER	0	1	0	2	0
CDER	2	0	0	2	1
CDRH	0	2	0	2	1

Tables 4 and 5 provide timeliness data by the product type of the issued RFD decisions.

Table 4. Timeliness of Combination Product Determinations.

Determination	Product Assignments Issued*	Percent On Time*
Drug-Device	5	100%
Drug-Biologic	0	NA
Device-Biologic	1	100%
Drug-Device-Biologic	1	100%
Total	**7**	**100%**

* Does not include Request for Reconsideration responses which are issued within the 15-day time frame provided by 21 CFR 3.8. No Requests for Reconsideration were submitted for a combination product in FY 2020.

Table 5. Timeliness of Non-Combination Product Determinations.

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

* Does not include Request for Reconsideration responses, which are issued within the 15-day time frame provided by 21 CFR 3.8. No Requests for Reconsideration were submitted for a non-combination product in FY 2020.

Pre-RFD Workload Performance Results

Now in its fourth formalized program year, OCP continues the Pre-RFD program[14] to provide preliminary feedback to Pre-RFD submissions for product classifications and Center assignments (i.e., Pre-RFD assessments). The Pre-RFD process offers more flexibility than the RFD process, allowing for more discussions between FDA and a sponsor if questions arise during the review. Table 6 shows OCP's Pre-RFD submission review workloads from FY 2017 to FY 2020.

Table 6. OCP's Pre-RFD Workloads from FY 2017 to FY 2020.

Pre-RFD Assessments	FY 17	FY 18	FY 19	FY 20
Combination Product Assessments	44	48	51	47
Non-Combination Product Assessments	34	28	29	30
Unclassified Assessments*	0	6	3	2
Total Pre-RFD Assessments	78	82	83	79

* Pre-RFD assessments may not result in the classification of a product 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 Act and 21 CFR part 1271 or the sponsor for these products may have pursued a product assignment and not a classification.

Of the 79 total Pre-RFD assessments completed by OCP in FY 2020, 72 (92 percent) were issued by OCP's internally established 60-day goal date that begins when OCP receives sufficient information to provide the requested feedback.[9] The average review time for Pre-RFD submissions was 55.7 days, with a median review time of 59 days. The following tables (i.e., Tables 7 through 10) provide data on the Pre-RFD assessments for combination products and

[14] 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 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.

non-combination products based on the products' classification and the Center assignment.

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

Classification	Pre-RFDs Issued	Percent Issued in 60 Days[9]
Drug-Device	37	92%
Drug-Biologic	1	100%
Device-Biologic	6	83%
Drug-Device-Biologic	3	100%
Total	47	91%

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

Center Assignment	Pre-RFDs Issued	Percent Issued in 60 Days[9]
CDER	33	91%
CBER	6	83%
CDRH	8	100%
Total	47	91%

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

Classification	Assignments Issued	Percent Issued in 60 Days[9]
Drug	15	93%
Biologic	5	80%
Device	10	100%
Total	30	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[9]
CDER	16	94%
CBER	6	83%
CDRH	8	100%
Total	30	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., Classification and Center-Assignment Consultations (CCA Consults)) and other FDA offices. For instance, Centers may contact OCP for assistance in determining whether 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 submitted to OCP is presented in Table 11.

Table 11. Number of CCA Consults by Center from FY 2018 to FY 2020.

Center Assignment	FY 18	FY 19	FY 20
CDER	31	51	44
CBER	3	4	4
CDRH	13	14	27
Unassigned*	2	4	4
Total	50	73	79

* 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 solely concerns 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., whether it is acceptable to evaluate the PMOA). These activities also include responding to individual e-mail queries and holding meetings and teleconferences with sponsors, which may lead to RFDs/Pre-RFDs or obviate the need for them. In FY 2020, the number of these activities was nearly twice that of the previous 2 years. There was not an apparent explanation for the increase in activities (e.g., the activity increase was not SARS-CoV-2- or COVID-19-related).

Table 12. Number of OCP's Additional Product Classification and Center-Assignment Activities from FY 2018 to FY 2020.

	FY 18	FY 19	FY 20
Jurisdiction/Classification Activities[15]	529	463	950

OCP's FY 2020 Activities and Accomplishments

Table 13 highlights OCP's Activities for classification and Center-assignment for FY 2020.

Table 13. Specific FY 2020 Activities by OCP.

Type of Activity	FY 2020 Activities
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 (1) clarifying standards for cross-

[15] In FY 2021, OCP is working to enhance its ability to track inquiries and other activities, which will likely enable a more granular assessment of the queries received and the ability to identify topics that may warrant more guidance.

Type of Activity	FY 2020 Activities
	labeled combination products' statuses, (2) clarifying the regulatory status of software used with a drug or biological product, (3) determining when container/closures are also considered devices, and (4) classifying articles that meet both the biological product and device definitions.
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 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 responsibility includes overseeing the timeliness of reviews, the consistency of FDA's 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 (also referred to as "inter-Center consult requests" in this document). These procedures were formally incorporated into the FDA Staff Manual Guide (SMG) 4101 (titled "Inter-Center Consult Request Process"). FDA updated this SMG in June 2018 to improve inter-Center coordination for combination products and to enhance the timeliness and consistency of inter-Center reviews.

Consistent with OCP's mandates under the Cures Act, in FY 2020, FDA continued its efforts to improve the inter-Center consult process for combination products, including completing 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 fora. These efforts have been used to identify opportunities for improvements in the inter-Center consult process, FDA's IT systems, FDA's staffing utilization, and the resources available to staff. OCP also continued to lead some and support other Agency efforts to develop and publish regulations, issue guidance documents, and develop other public-facing documents regarding the premarket review of combination products (as discussed more fully in the "Policy Activities and Accomplishments" section below).

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 2020 by CBER, CDER, and CDRH (including submissions filed or received in FY 2020), 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 Prescription Drug User Fee Act Reauthorization of 2017 (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 abbreviated new drug applications (ANDAs), and the Biosimilar User Fee Amendments (now BsUFA II) goals were referenced for the 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 results 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 2015 to FY 2020

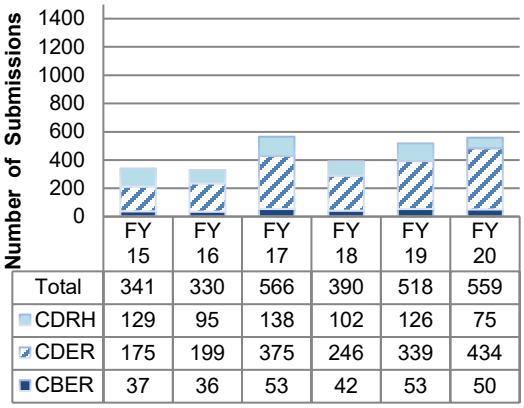
As shown in Table 14, 559 original applications were submitted for review in FY 2020.

Table 14. FY 2015 to FY 2020 Submission Review Workloads.

Submission/ Request	FY 15	FY 16	FY 17	FY 18	FY 19	FY 20
Total Combination Products Submitted for Review	341	330	566	390	518	559

As reflected in Table 15, of all combination product submissions, 78 percent were received by CDER, 13 percent were received by CDRH, and 9 percent were received by CBER.

Table 15. Combination Product Application Submissions by Center.



	FY 15	FY 16	FY 17	FY 18	FY 19	FY 20
Total	341	330	566	390	518	559
CDRH	129	95	138	102	126	75
CDER	175	199	375	246	339	434
CBER	37	36	53	42	53	50

Table 16 presents the 559 original applications for combination products received in FY 2020, broken down by the identified 10 application types and by the product's initial classification into one of nine categories of combination products.[16] The same table reflecting applications received in FY 2019 has been updated in Appendix A to reflect corrections and actions as of September 30, 2020. The majority of the applications received in FY 2020 were original investigational new drug applications (INDs) (67 percent), followed by ANDAs (11 percent). Also, the most common combination product category was the possible combination based on the mutually conforming labeling of separate products (20 percent).

Table 16. Workload by Combination Product Category Number.

Application Type	1	2	3	4	5	6	7	8	9	Totals
Original NDAs	13	11	0	0	0	0	0	0	2	26
Original BLAs	1	0	11	0	0	1	2	0	1	14
Original PMAs	1	0	0	0	0	0	0	0	0	1
Original 510(k)s	4	0	0	29	1	0	2	2	0	38
Original INDs	29	41	59	6	8	96	3	102	29	373
Original Investigational	0	0	0	16	9	0	7	5	7	44

[16] 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).

Device Exemptions (IDEs)										
Original Humanitarian Device Exemptions (HDEs)	0	0	0	0	0	0	0	0	0	0
Original ANDAs	18	45	0	0	0	0	0	0	0	63
Biosimilar BLAs	0	0	0	0	0	0	0	0	0	0
De Novos	0	0	0	0	0	0	0	0	0	0
Totals	66	97	70	51	18	97	12	109	39	559

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

Inter-Center Consult Requests

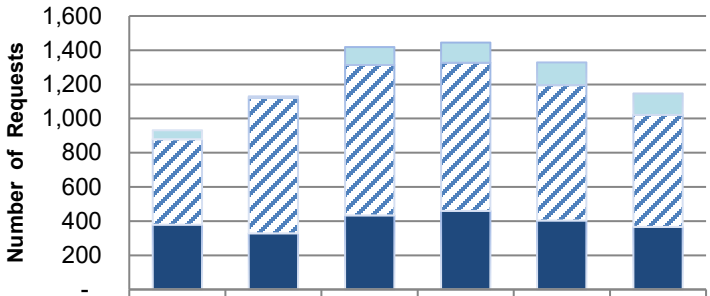
This section reports on the number of inter-Center consults for combination products, a related but distinct topic from the number of submissions for combination products. There can be, for example, multiple consults for a single combination product submission or a submission may not warrant a consult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

CDRH consult topics include human factors/user interfaces and software.[17]

OCP monitors the performance of the inter-Center consult process for correctness (e.g., ensuring the information in the consult requests are complete, confirming the requests are being directed to the correct recipient, etc.) and timeliness (e.g., ensuring that consults allow the recipient adequate time to complete the request while accounting for the established product review goals, etc.). OCP works with CBER, CDER, and CDRH in identifying potential areas of improvement and implementing changes to improve the consult process.

In FY 2020, there were 1,146 inter-Center consults for combination products. Table 17 shows the number of FY 2020 inter-Center consults requested by each of the three medical product Centers.

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



	FY 15	FY 16	FY 17	FY 18	FY 19	FY 20
Total	932	1,130	1,419	1,445	1,328	1,146
CBER	53	9	105	118	133	124
CDER	499	793	881	867	792	656
CDRH	380	328	433	460	403	366

In Table 18, the total number of inter-Center consults in FY 2020 is compared to the previous 5 years.

[17] 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 but are often conducted under the same process outlined in SMG 4101 (www.fda.gov/media/81927/download).

Table 18. FY 2015 to FY 2020 Inter-Center Consult Workloads.

Submission/Request	FY 15	FY 16	FY 17	FY 18	FY 19	FY 20
Total Inter-Center Consult Requests	932	1,130	1,419	1,445	1,328	1,146

In Table 19, the number of inter-Center consult requests during FY 2020 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	--	29	95	124
CDER	19	--	637	656
CDRH	6	360	--	366
Total	25	389	732	1,146

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	--	79	--	79
BLA	6	70	--	76

Investigational New Drug Application (IND) / Pre-IND	100	380	--	480
NDA	1	123	--	124
510(k)	1	--	4	5
De Novo	--	--	11	11
Investigational Device Exemption (IDE)	--	--	87	87
PMA	2	--	76	78
Pre-Submission	1	--	182	183
Other	13	4	6	23
Total	124	656	366	1,146

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

Timeliness in Days of the Reviews of Combination Products

FDA is required to report the timeliness of its reviews of combination products. Table 21 summarizes the review types and applicable review performance targets for original NDAs, ANDAs, Prescription Drug User Fee Act 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. Combination products are subject to the same review performance targets as noncombination products, which are determined based on the premarket review application type and the User Fee Program to which the application is subject. 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 without Pre-Submission Facility Correspondence	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 approach 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 2019 and FY 2020 Review Performance Results," updates FDA's final review performance results on the FY 2019 combination product submissions and presents FDA's preliminary review performance results on the FY 2020 combination product submissions through September 30, 2020.

FY 2019 and FY 2020 Review Performance Results

Table 22 shows the final FY 2019 review goal performance results.

Table 22. Final FY 2019 Review Goal Performance Results.

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 318
NDAs	Standard	10 Months	26	304	297 to 452
BLAs	Priority	6 Months	2	134.5	113 to 156
BLAs	Standard	10 Months	362	334	285 to 366
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	63	295	241 to 309
ANDAs	Priority without Pre-Submission Facility Correspondence	10 Months	39	298	273 to 350
ANDAs	Priority with Pre-Submission Facility Correspondence	8 Months	7	240	224 to 242
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 2020 review goal performance results through September 30, 2020.

Table 23. Preliminary FY 2020 Review Goal Performance Results.

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	59 to 244
NDAs	Standard	10 Months	5	305	304 to 388
BLAs	Priority	6 Months	1	226	226
BLAs	Standard	10 Months	1	364	364
Expedited and Original PMAs	Standard	180 or 320 Days[†]	1	189	189
510(k)s	Standard	90 Days	38	88	0 to 103
Biosimilar BLAs	Standard	10 Months	0	N/A	N/A
ANDAs	Standard	10 Months	93	298	91 to 323
ANDAs	Priority without Pre-Submission Facility Correspondence	10 Months	9	298	116 to 203
ANDAs	Priority with Pre-Submission Facility Correspondence	8 Months	6	241	233 to 269
De Novos	Standard	150 Days	0	N/A	N/A

[†] 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 or procedural challenges. OCP fosters early interactions between sponsors and FDA to help clearly delineate the regulatory pathways for the development of combination products and to help ensure the expeditious review of 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, including topics spanning the developmental and review process across all submission types. 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. In addition, OCP leads or participates in product-specific meetings and discussions to ensure efficient, effective communication between sponsors and FDA review staff, to align data expectations for products raising similar regulatory questions, and to respond to regulatory questions related to combination products.

The number of OCP's product-specific documented premarket review actions from FY 2015 to FY 2020 are presented in Table 24.

Table 24. Number of OCP's Documented Premarket Activities from FY 2015 to FY 2020.

	FY 15	FY 16	FY 17	FY 18	FY 19	FY 20
Premarket Review Activities	225	266	525	321	144	188

In FY 2020, as shown in Table 24, OCP received 188 requests for product-specific assistance, the responses to which contributed to ensuring the timely, effective, and aligned review of combination products.[18] Notably, in FY 2020, OCP addressed issues including the following:

- For SARS-CoV-2- or COVID-19-related product development, OCP provided rapid support to the Centers in developing (1) responses to the sponsor about the classification and assignment of the applicable product and (2) guidance relevant to that product;

- Clarification of submission pathways and related development considerations for generic combination products;

- Novel drug and biological products combined with new technological delivery systems that may have unique risk profiles;

- Alignment of pharmacology/toxicology and biocompatibility data requests to sponsors;

[18] Decreases in OCP's premarket activities have coincided with FDA's ongoing implementation of the updated inter-Center consult request processes, launched in FY 2018 and FY 2019, which include updating IT systems, enhancing training, and providing other resources for Centers' staff.

- Regulatory considerations for the review of combination products for rare disease populations;

- Cross-Center consistency for potential clinical hold or approvability review assessments;

- Accuracy, consistency, and clarity of the labeling of separately distributed products intended for combined use; and

- Development and labeling considerations for combination products that incorporate mobile communication technologies or digital health innovations.

In addition, OCP oversees and facilitates coordination among review Centers under the inter-Center consult process to, for example, ensure that reviews of premarket applications are completed in a timely manner and meet applicable user fee timelines. 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 statuses; facilitates access to review documents; and works to resolve other barriers to the timely completion of consults. OCP periodically reviews inter-Center consult request data 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 (i.e., communications and/or clarification of product-specific review findings) in resolving Center timeliness issues.

OCP facilitates the resolution of master file review communication uncertainties. Also, OCP hosts premarket meetings with industry and Agency subject-matter experts to provide clarifications on the use of master files for combination products.

OCP participated in database test sessions and implementation discussions to ensure continued cross-Center access and usability of a new CDER/CBER electronic submissions database. Also, OCP provided recommendations to ensure consistent CDRH access to the new database and promoted training of this database to CDRH reviewers.

In addition, OCP assists the Centers and industry on regulatory and scientific issues relating to specific combination products or to specific categories of combination products. Examples of these activities during FY 2020 are presented in Table 25.

Table 25. OCP's Provision of Significant Premarket Review Facilitation or Assistance During FY 2020.

Type of Activity	FY 2020 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 or treatment selection technologies; • Injector delivery systems (e.g., intrathecal and on-body-wearable pump infusion 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; • Implication of packaging changes during product development; • 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 certain combination products; and • Facilitation of industry and Agency review teams for clarification of human factors considerations.

Combination Product Postmarket Activities

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

OCP meets the postmarket regulation requirement by undertaking a variety of compliance-related and postmarket activities to help ensure the safety and quality of combination products. These activities include leading the Agency's efforts to develop and publish regulations, guidances, and other public-facing documents regarding postmarketing safety reporting (PMSR) requirements 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. In addition to policy work, OCP may provide support for FDA's CGMP facility inspections and the inspection of products at ports of entry, assist in responding to product-specific safety signals and defect issues, or offer guidance on compliance and enforcement actions. 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 2020 product-specific actions related to the consistency and appropriateness of postmarket regulatory activities are reflected in Table 26.

Table 26. Documented Product-Specific Postmarket Regulatory Activities from FY 2015 to FY 2020.

	FY 15	FY 16	FY 17	FY 18	FY 19	FY 20
Postmarket Regulatory Activities	71	50	74	86	62	113

OCP engaged in 113 product-specific, postmarket-related matters involving issues such as the application of CGMP and quality system regulations for inspections of combination products, the appropriate mechanisms and responsibilities for reporting adverse events, and the requirements

for facility registration and product listing. [19] 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:

- Clarifying stakeholders' and FDA's understanding of the combination product CGMP inspectional approach (see also the discussion of a final compliance program under the "Policy Activities and Accomplishments" section below); and

- Facilitating the implementation of the PMSR final rule[20] requirements through the creation of updates to the systems and the development of both tools for postmarket staff and other resources for regulated entities that clarify how to prepare compliant reports.

[19] The increase in FY 2020's postmarket regulatory activities largely reflects an unusually high volume of technical inquiries relating to coming into full compliance with the 2016 final rule on PMSR for combination products by July 31, 2020, in accordance with the Compliance Policy for the rule (www.fda.gov/files/about%20fda/published/compliance-policy-combination-product-postmarketing-safety-reporting.pdf). The Compliance Policy delayed full enforcement of the rule in light of substantive stakeholder input supporting the need for such delay to ensure applicants sufficient time to update reporting and recordkeeping systems and procedures, including their IT systems.

[20] 81 FR 92603 (Dec. 20, 2016).

Effective Resolutions of Review Disputes

When OCP receives a formal request by a sponsor to resolve a dispute regarding the timeliness of the premarket review of a combination product, OCP must resolve the dispute. OCP also facilitates communications between sponsors and FDA review staff to identify, clarify, and resolve specific concerns associated with review timeliness. This facilitation helps prevent the need for 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 the intent of a review division's decision or in resolving differences of view regarding regulatory requirements).

Percentage of Combination Products Reviewed for Which A Formal Dispute Resolution Was Requested

FDA is required to identify the percentage of combination products for which dispute resolution with respect to premarket review was requested by the combination product's sponsor. FDA received no formal requests for dispute resolution for combination products in FY 2020. 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 provide examples of informal facilitation and resolution of issues by OCP related to premarket review.

Policy Activities and Accomplishments

OCP's policy activities include leading and assisting with policy initiatives important to the regulation of combination products. Examples of such activities pursued in FY 2020 are discussed below and included in the tables to follow.

Supporting and Implementing 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, the enhancement of standard operating procedures, the development of improvements to the IT system, the training of staff, and an 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 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,[21] to update and clarify the regulations in light of legislative and other policy developments.

Clarifying Regulatory Policy

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

- Draft guidance on requesting FDA's feedback on combination products (guidance has since been finalized) (12/2020)[22]
- Draft guidance on drug master files for drug-led combination products including

[21] Available at www.federalregister.gov/documents/2018/05/15/2018-10321/product-jurisdiction.

[22] Available at www.fda.gov/regulatory-information/search-fda-guidance-documents/requesting-fda-feedback-combination-products.

electronics or software (10/2019)[23]

- Draft guidance on bridging for drug-device and biologic-device combination products (12/2019)[24]
- Draft guidance on peripheral percutaneous transluminal angioplasty and specialty catheters – premarket notification 510(k) submissions (01/2020)[25]
- Final rule on the definition of "protein" for purposes of the statutory definition of "biological product" (2/2020)[26]
- Draft guidance on restricted delivery systems: flow restrictors for oral liquid drug products (3/2020)[27]
- Draft guidance on the technical considerations for demonstrating the reliability of emergency-use injectors submitted under a BLA, NDA, or ANDA (04/2020)[28]
- *Federal Register* notice announcing the Agency's intention not to pursue a "devices referencing drugs" potential approach for sponsors seeking marketing authorization for devices labeled for a new use with an approved, marketed drug (5/2020)[29]
- Final guidance on postmarketing adverse event reporting for medical products and dietary supplements during a pandemic (5/2020)[30]
- Compliance Program 7356.000 Inspection of CDER-led or CDRH-led combination products (06/2020)[31]
- Final guidance on multiple function device products: policy and considerations (7/2020)[32]
- Final guidance on regulatory considerations for human cells, tissues, and cellular and tissue-based products: minimal manipulation and homologous use (7/2020)[33]

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[23] Available at www.fda.gov/regulatory-information/search-fda-guidance-documents/type-v-dmfs-cder-led-combination-products-using-device-constituent-parts-electronics-or-software.

[24] Available at www.fda.gov/regulatory-information/search-fda-guidance-documents/bridging-drug-device-and-biologic-device-combination-products.

[25] Available at www.fda.gov/regulatory-information/search-fda-guidance-documents/peripheral-percutaneous-transluminal-angioplasty-pta-and-specialty-catheters-premarket-notification.

[26] Available at www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/definition-term-biological-product-final-regulatory-impact-analysis.

[27] Available at: www.fda.gov/regulatory-information/search-fda-guidance-documents/restricted-delivery-systems-flow-restrictors-oral-liquid-drug-products-guidance-industry.

[28] Available at www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-demonstrating-reliability-emergency-use-injectors-submitted-under-bla-nda.

[29] Available at www.federalregister.gov/d/2020-09832.

[30] Available at www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarketing-adverse-event-reporting-medical-products-and-dietary-supplements-during-pandemic.

[31] Available at www.fda.gov/media/138592/download.

[32] Available at www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-function-device-products-policy-and-considerations.

[33] Available at www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal.

Other Policy-Related Activities

Additional policy-related activities included the following:

- Enhancement of procedures and mechanisms for monitoring and enhancing combination products' premarket and postmarket regulatory activities, consistent with section 3038 of the 21st Century Cures Act;
- Continued the performance of evaluations and updates of procedural and IT systems to enable the implementation of the final PMSR rule for combination products;
- Development and provision of training on the PMSR requirements to FDA's medical product Centers' product safety offices and other staff involved with addressing safety signals; and
- Development and provision of training on the compliance program for combination product CGMPs to inspectors in Office of Regulatory Affairs' medical product programs and to medical product Center staff involved with manufacturing and compliance activities.

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

Table 27. Additional Jurisdictional Regulatory Initiatives.

Type of Activity	FY 2020 Activities
Developing regulations and guidance	OCP jurisdiction-related activities included participating in the following Agency rulemaking and guidance initiatives: • Rulemaking and associated policy activities relating to the meaning of "protein" in the definition of "biological product" in the Public Health Service Act[34] • Cross-Center working group on the scope and significance of cross-labeled combination product status
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 • Development of a classification policy for tissue and cellular products

[34] Available at www.govinfo.gov/content/pkg/FR-2019-12-12/pdf/2019-26840.pdf.

Table 28. Additional Premarket Review Regulatory Initiatives.

Type of Activity	FY 2020 Activities
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 the technical aspects of intravaginal system combination products. • OCP chaired a cross-Center working group to develop a guidance for the technical considerations for demonstrating the reliability of combination product emergency-use injectors. • OCP led a cross-Center working group to complete a Cures Act-mandated guidance on obtaining feedback from FDA for combination products through application-based meetings and combination product agreement meetings. • OCP led a cross-Center working group to develop a guidance on essential performance requirements. • OCP continued to lead a cross-Center working group on insulin pump labeling considerations. • OCP also led efforts to finalize a guidance on premarket principles and pathways for combination products, update a guidance on the application of user fees for combination products, develop a revised draft guidance on postmarket changes for combination products, and revise inter-Center agreements on medical product assignment/coordination. OCP participated in the development of the following policy documents: • Rulemaking on De Novo classification • Comments for citizen petition responses for specific types of generic combination products

Type of Activity	FY 2020 Activities
	• Technical considerations for the visual inspection of particulates in injectable solutions • Considerations for what constitutes clinical data for user fee purposes • Technical considerations for container closures that are also device constituent parts • Final rule on importation of prescription drugs • Final guidance on importation of prescription drugs • Proposed rule to amend part 820 to align more closely with International Organization for Standardization (ISO) 13485 and associated amendments to part 4 • International Council for Harmonisation's (ICH's) Q12 implementation guidance
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: • Non-prescription drug availability • The Agency's thinking on the regulation of certain software output as drug labeling • Issues such as importation of prescription drugs, good guidance practices, and enforcement policies • Considerations for compounded drugs for use with devices
Conducting procedural oversight and facilitation	OCP led a working group regarding the monitoring and continuous improvement of the inter-Center consult process, including IT development and enhancement.

Table 29. Additional Postmarket Review Regulatory Initiatives.

Type of Activity	FY 2020 Activities
Participating in other Inter-Center and Agency-wide working groups to clarify issues related to combination products	• OCP continued to chair working groups relating to the PMSR requirements for combination products. This work focused on implementation of the rule, including developing a Memorandum of Understanding for engagement between the Centers and OCP on postmarket combination product issues and developing and delivering internal training. • OCP continued to lead activities to support implementation of CGMP requirements for combination products, including developing and issuing a compliance program for inspection of CDER-led and CDRH-led combination products, training inspectional and compliance staff, and finalizing a notice on CGMP alternatives/flexibilities. • 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 IT initiatives to enhance the infrastructure and improve the efficiency, consistency, and reliability of information systems and communications within and across Agency components and with stakeholders.

- OCP implemented four enhancement releases in FY 2020 to improve the Inter-Center Consult Request workflow and data capture, including changes to promote consistency in postmarketing consult requests for combination products.

- In light of the final rule on PMSR for combination products, OCP launched a new technology platform to integrate, to the extent feasible, data on combination products from different data sources—such as premarket systems, registration and listing systems, 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.

- OCP launched a new electronic system to harmonize the workflow and data capture for Pre-RFDs and RFDs. OCP also conducted a formal pilot with external volunteers of a new Pre-RFD and RFD electronic submission process to improve the efficiency and completeness of these submissions.

- OCP provided training, demonstrations, user guides, and other resources to new users from all three human medical product Centers for all OCP-led systems.

External Outreach

OCP conducted outreach on FDA's classification, assignment, and regulation of combination products by engaging with trade associations and coalitions (e.g., Combination Products Coalition, Advanced Medical Technology Association, the Pharmaceutical Research and Manufacturers of America, and the Biotechnology Innovation Organization), representing the drug, device, biological product, and combination product industries. In addition, OCP participated in national and international standards development organizations, including co-chairing a committee on combination products for the Association for Advancement of Medical Instrumentation and supporting the work of ISO, ICH, International Medical Device Regulators Forum, and ASTM International. OCP also presented at various industry conferences.

FDA addressed a wide range of topics about which stakeholders have questions, concerns, or proposals for Agency consideration. Topics included 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 2020 outreach activities via industry conferences are included in Table 30.

Table 30. Examples of FY 2020 Outreach Activities.

Type of Activity	FY 2020 Accomplishments
Presentations and outreach activities	The following are examples of venues/events for which OCP provided presentations and/or educational outreach: • Drug Information Association (DIA) Combination Products Conference (October 2019) • Xavier University Health Combination Products Summit (October 2019) • Combination Products Forum, Berlin, Germany (October 2019) • Regulatory Association Professional Society (RAPS) Combination Products PMSR Workshop (November 2019) • International Society of Pharmaceutical Engineers (ISPE) Global Pharmaceutical Regulatory Summit (December 2019) • Pharmaceutical Development Association (PDA) Optimizing Quality Risk Management Conference (December 2019) • DIA Short Course on Pharmacovigilance for Medication Errors (January 2020) • DIA Advertising and Promotion Regulatory Affairs Conference (May 2020) • FDA Small Business Information Association (SBIA) Regulatory Education for Industry: Pharmacovigilance and Risk Management Conference (June 2020) • Combination Products: Reporting Device Information and Malfunctions, FDA SBIA Regulatory Education for Industry: Pharmacovigilance and Risk Management Conference, Webinar (June 2020) • TOPRA/RAPS Inter-regulatory and Stakeholder Workshop on Alignment of Global Combination Products Regulations

Type of Activity	FY 2020 Accomplishments
	(June 2020) • ISPE: Roadmap of the Pathways for Combination Products (August 2020) • DIA/FDA “Workshop on complex generic drug-device combination products” – Steering Committee to develop the October 2020 workshop • PDA Delaware Valley Chapter and West: The Evolving Landscape for Combination Products Defining a Regulatory Strategy (September 2020) • RAPS 2020: Convergence (September 2020) • Global Bio Conference 2020, Sponsored by Korean Ministry of Food and Drug Safety (September 2020)

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Appendix A: FY 2019 Updated Performance Detail

The table below reflects the 519 original applications classified into one of nine categories of combination products received in FY 2019.

Workload by Combination Product Category Number.

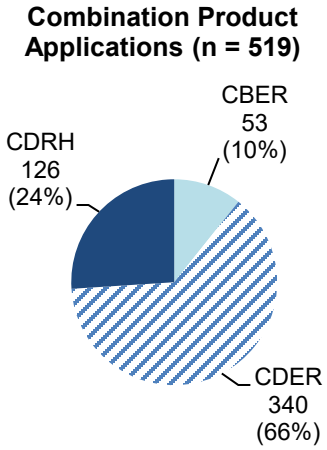
Application Type	1	2	3	4	5	6	7	8	9	Totals
Original NDAs	16	16	0	0	0	0	0	0	0	32
Original BLAs	2	0	4	0	0	2	2	0	0	10
Original PMAs	0	0	0	4	0	0	1	0	0	5
Original 510(k)s	18	0	0	63	1	0	8	0	0	90
Original INDs	20	32	27	1	12	54	11	87	19	263
Original IDEs	3	0	0	14	1	0	4	5	3	30
Original HDEs	0	0	0	0	0	0	0	0	0	0
Original ANDAs	27	56	0	0	0	0	0	0	0	83
Biosimilar BLAs	0	0	5	0	0	0	0	0	0	5
De Novos	0	0	0	0	0	0	0	0	0	0
Totals	86	104	36	83	14	56	26	92	22	519

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 2019 by Center lead, as of September 30, 2020.



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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on OCP's home page at https://www.fda.gov/combination-products.