Performance Report to Congress

Office of Combination Products

FY 2021

(as required by the Medical Device User Fee and Modernization Act of 2002)

Commissioner's Report

I am pleased to submit the fiscal year 2021 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 18th full year since OCP was established, which was mandated by the Medical Device User Fee and Modernization Act of 2002 (P.L. 107-250) that was enacted on October 26, 2002. Despite the challenges presented by the COVID-19 pandemic, including a reprioritization of FDA's activities and an increased workload, OCP has continued to fulfill its responsibilities relating to its jurisdiction of, premarket review of, and postmarket oversight of combination products.

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 (that is, 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. Therefore, these products can raise complex regulatory, policy, and review management challenges. For instance, 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. These aspects include preclinical testing, clinical investigation, marketing application review, manufacturing and quality control, adverse event reporting, promotion and advertising, user fees, and post approval modifications.

OCP continues to enhance the efficiency, consistency, transparency, and predictability of its processes for assigning combination products to the appropriate lead Center. 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.

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.

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

Executive Summary

The U.S. Food and Drug Administration (FDA or 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 includes ensuring (1) the prompt assignment of combination products (drug-device, biologic-device, drug-biologic, or drug-device-biologic products)[1] 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.

This annual performance report to Congress covers OCP's activities and accomplishments during fiscal year (FY) 2021 (i.e., October 1, 2020, to September 30, 2021). This report highlights the following OCP activities for FY 2021:

A. Prompt Assignment of Combination Products

Companies may submit Request for Designation (RFD) submissions to obtain formal Agency determinations for the classification of a human medical product (e.g., biological product, device, drug, or combination product) and/or for the Center assignment (i.e., the lead Center in the case of a combination product) for the product's premarket review and regulation. In FY 2021, OCP issued one combination product and two non-combination product RFD decisions, with every classification and/or assignment decision meeting FDA's 60-day statutory requirement for decisions. Alternatively, companies may submit a Pre-Request for Designation (Pre-RFD) to obtain informal feedback from OCP on a product's classification and/or Center assignment. In FY 2021, OCP provided classification and Center assignment feedback for 46 Pre-RFDs. (For more information, see the "Policy and Procedural Activities and Accomplishments" section below.)

B. Timely and Effective Combination Product Premarket Review

In FY 2021, OCP conducted several activities related to the premarket review of combination products. For instance, OCP received 124 requests for product-specific premarket assistance, the responses to which contributed to ensuring FDA's timely, effective, and aligned review of combination products. FDA's efforts enabled sponsors to expeditiously address FDA's concerns and bring products to market more efficiently, thereby expediting patient access to new treatment options. In addition, OCP chaired and/or participated 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. Further, in FY 2021, FDA received 596 original premarket applications for combination products. There were 1,202 inter-Center consulting

[1] Examples of combination product types can be found on the Combination Products website, which is available at http://www.fda.gov/CombinationProducts/default.htm.

reviews for combination products in FY 2021. (For more information, see the *Policy and Procedural Activities and Accomplishments* section below.)

C. Consistent and Appropriate Postmarket Regulation

In FY 2021, OCP provided clarification and support for 84 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. OCP also continued to work with the human medical product Centers on registration and listing issues, postmarket manufacturing compliance, and other postmarket regulatory issues pertaining to specific combination products. These various efforts furthered FDA's capabilities to identify and help mitigate potential risks to patients associated with products currently on the market. (For more information, see the "Policy and Procedural Activities and Accomplishments" section below.)

D. Policy and Procedural Activities and Accomplishments

In FY 2021, OCP continued to implement section 3038 of the 21st Century Cures Act and to develop policy regarding complex regulatory and procedural questions for combination products. OCP also continued to develop policy related to both (1) separately distributed medical products intended for combined use that are not combination products and (2) the classification and assignment of challenging 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 in FY 2021 to support OCP's related activities, some of which are detailed below.

For example, FDA issued a *Federal Register* notice[2] regarding a decision by the U.S. Court of Appeals for the District of Columbia Circuit in *Genus Med. Techs., LLC v. FDA*, 994 F.3d 631 (D.C. Cir. 2021), which held that FDA cannot classify as a *drug* any product that meets the *device* definition in section 201(h) of the Federal Food, Drug, and Cosmetic Act. The notice (1) announced FDA's intent to establish a process for making an orderly and efficient determination of which products currently regulated by FDA as *drugs* must now be regulated as *devices* under *Genus* and (2) solicited public comment on this process. In addition, FDA issued a *Federal Register* notice regarding consolidating its regulatory oversight responsibilities in the Center for Biologics Evaluation and Research for certain devices that process autologous human cells, tissues, and cellular and tissue-based products (HCT/Ps) at the point of care where the device output is intended to mediate the intended therapeutic effect.[3] Further, OCP continued to develop policies related to the following topics: human factors, essential performance requirements, principles of premarket pathways for combination products, regulatory

[2] 86 FR 43553 (Aug. 9, 2021), available at https://www.federalregister.gov/public-inspection/2021-16944/request-for-information-genus-medical-technologies-llc-versus-food-and-drug-administration.

[3] 86 FR 50887 (Sept. 13, 2021), available at https://www.federalregister.gov/documents/2021/09/13/2021-18912/consolidation-of-devices-that-process-autologous-human-cells-tissues-and-cellular-and-tissue-based

considerations for cross-labeled combination products and other separately distributed medical products intended for combined use, alternative mechanisms to address current good manufacturing practice expectations, and unique identifiers for combination products. Also, OCP issued system updates and training to enhance not only the efficiency of the inter-Center consult process but also access to relevant postmarket information via an online "dashboard."

OCP also continued, in FY 2021, to conduct external outreach activities through engagement with stakeholder organizations and through a variety of educational and informational presentations to national and international audiences and standard-setting bodies. These activities were intended to foster a greater understanding of the complex regulatory and scientific issues in the developmental, premarket, and postmarket settings for combination products; clarify how stakeholders can engage with FDA on these issues; enable FDA to understand and consider stakeholders' questions and concerns; and identify potential areas for regulatory convergence across jurisdictions for FDA's oversight of combination products.

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Acronym List

510(k)	Premarket Notification
ANDA	Abbreviated New Drug Application
BLA	Biologics License Application
BsUFA	Biosimilar User Fee Act
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
FDA	Food and Drug Administration
FY	Fiscal Year (October 1 to September 30)
GDUFA	Generic Drug User Fee Act
HDE	Humanitarian device exemption
ICH	International Council for Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug
IT	Information Technology
MDUFA	Medical Device User Fee Amendments
MDUFMA	Medical Device User Fee and Modernization Acct 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

I. 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.[4]

A. 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

[4] Available at http://www.fda.gov/CombinationProducts/default.htm.

investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Some combination products (1) have the potential to provide enhanced therapeutic advantages compared to non-combination medical products[5] (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 technologies and scientific advancements.

B. 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 oversight and facilitative duties relating to the premarket review and postmarket oversight of combination products.[6] However, the primary day-to-day responsibilities for the 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;

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[5] Throughout this document, the terms "medical product" and "human medical product" may be used interchangeably, and they refer to human medical products regulated by the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, or the Center for Devices and Radiological Health.

[6] 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, is available at https://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 the Agency's ongoing efforts to improve and enhance these practice areas. OCP continues to implement the recommendations as discussed in this FY 2021 Performance Report.

(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.

OCP serves as a focal point for addressing combination product issues raised by FDA's reviewers and stakeholders and works with the relevant Centers not only to develop guidance documents, regulations, processes, and procedures but also to enhance the clarity, transparency, efficiency, effectiveness, and consistency 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.

C. Performance Results Presented in This Report

This report presents OCP's FY 2021 activities and accomplishments, including its fulfillment of statutory mandates. This report presents information and data on OCP's activities related to the following:[7]

- Prompt assignment of combination products
    - Timeliness of the classification and 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

[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 implementation of the Cures Act proceeds, the Agency will consider what additional information or adjustments may be appropriate for subsequent reports.

- Consistent and appropriate postmarket regulation
    - Efficient, effective, and consistent facility inspections
    - Efficient and effective product tracking and tracing
    - Timely consideration of safety signals
- Effective resolution of review disputes
    - Timeliness of dispute resolutions regarding combination products

Unless otherwise noted, all performance data are as of September 30, 2021.

II. Prompt Assignment of Combination Products

Companies may submit RFD submissions to obtain formal Agency determinations for the classification of a human medical product (e.g., biological product, device, drug, or combination product) and/or for the assignment of the lead Center for the product's premarket review and regulation.

OCP is required to formally respond to RFDs by classifying a product as a biological product, device, drug, or combination product, as well as to assign a particular product to a lead Center (i.e., CBER, CDER, or CDRH). For combination products, OCP assigns the Center with primary jurisdiction (the lead Center) 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. RFD decisions help sponsors understand the regulatory requirements applicable to their products.

In addition to the above activities, OCP provides informal classification and Center assignment responses to Pre-Request for Designation (Pre-RFD) submissions.[8] Further, OCP leads and/or supports other Agency efforts to develop and publish regulations, guidance documents, and policies related to the classification and assignment of medical products (which is discussed more fully in the "Policy Activities and Accomplishments" section below).

Frequently, sponsors submit RFDs or Pre-RFDs that are not sufficiently complete for FDA to file the submissions and conduct its assessment of the submissions. Many RFDs and Pre-RFDs require multiple rounds of filing review before they are accepted for review. In these situations, OCP continues to assist sponsors to help ensure they understand what information is needed for the product's classification and assignment, thereby helping ensure that RFD and Pre-RFD submissions will be complete for FDA's review.

A. Requirement Workload Trends: FY 2017 to FY 2021

OCP received 66 RFD submissions in FY 2021. In addition, OCP reviewed four RFD submissions that were carried over at the end of FY 2020. Of the 70 total RFD submissions that were reviewed in FY 2021, three submissions (4%[9]) had a decision issued, 61 submissions (87%) were found to have insufficient information for filing, and six submissions (9%) were withdrawn

[8] 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."

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

by the sponsor. Of the three RFD determinations, one was classified as a combination product and two were classified as non-combination products.[10]

In Table 1, the total number of RFD determinations (i.e., classifications and assignments for both combination and non-combination products) in FY 2021 is compared to the previous 5 years.

Table 1. RFD Determinations from FY 2017 to FY 2021.*

RFD Submissions	FY 16	FY 17	FY 18	FY 19	FY 20	FY 21
Total RFD Combination Product Classifications/ Assignments	2	5	8	7	7	1
Total RFD Non-Combination Product Classifications/ Assignments	2	3	0	6	2	2

* Over the reported 6-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.)

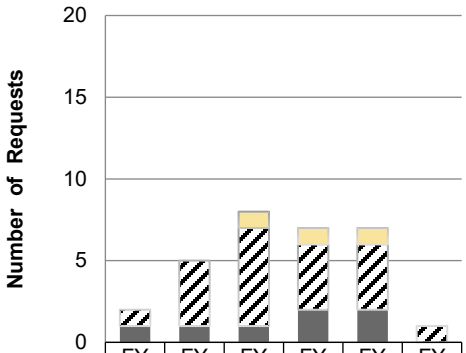
In FY 2021, the three RFD determinations were all issued by the statutorily mandated 60-day deadline. The average RFD review time was 59 days, with a median review time of 58.5 days. One RFD determination issued determined that the product was a device-biologic combination product type. Two RFD determinations issued determined that the products were non-combination product drugs.

[10] OCP did not receive any Requests for Reconsideration in FY 2021.

As shown in Table 2, the total number of RFD combination product determinations issued in FY 2021 decreased by six compared to FY 2020.

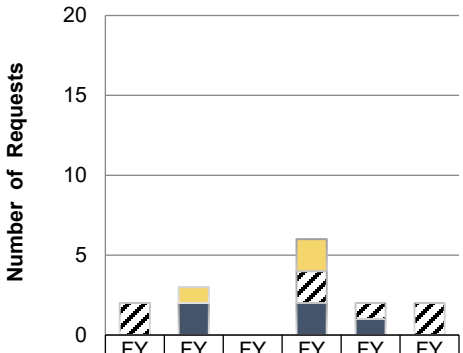
As shown in Table 3, the total number of RFD non-combination determinations issued in FY 2021 remained the same in FY 2020.

Table 2. Combination Product Assignment Determinations.



	FY 16	FY 17	FY 18	FY 19	FY 20	FY 21
Total	2	5	8	7	7	1
CBER	0	0	1	1	1	0
CDER	1	4	6	4	4	1
CDRH	1	1	1	2	2	0

Table 3. Non-Combination Product Assignment Determinations.



	FY 16	FY 17	FY 18	FY 19	FY 20	FY 21
Total	2	3	0	6	2	2
CBER	0	1	0	2	0	0
CDER	2	0	0	2	1	2
CDRH	0	2	0	2	1	0

1. Pre-RFD Workload Performance Results

Now in its fifth formalized program year, OCP continues the Pre-RFD program[11] to provide preliminary feedback 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 2021.

Table 6. OCP's Pre-RFD Workloads from FY 2017 to FY 2021.

Pre-RFD Assessment Decisions	FY 17	FY 18	FY 19	FY 20	FY 21
Combination Product Assessments	44	48	51	47	30
Non-Combination Product Assessments	34	28	29	30	15
Unclassified Assessments*	0	6	3	2	1
Total Pre-RFD Assessments	78	82	83	79	46

* 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 the 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.

A high percentage of Pre-RFDs cannot be filed because they lack sufficient information to initiate review. Of the 46 total Pre-RFD assessments completed by OCP in FY 2021, 28 (61%) were issued by OCP's internally established 60-day goal date that begins when OCP receives sufficient information to provide the requested feedback. The average review time for Pre-RFD submissions was 89.7 days, with a median review time of 60 days. Other filed Pre-RFDs either

[11] 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, responding to 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.

were withdrawn by their sponsors prior to OCP issuing its assessment recommendation or remain under review due to FDA's pending implementation of the *Genus* decision.[12]

Tables 7 through 10 provide data on FDA's Pre-RFD assessments for combination products and non-combination products based on the products' classification and the Center assignment.

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

Classification	Pre-RFDs Issued	Percent Issued in 60 Days
Drug-Device	22	68%
Drug-Biologic	0	N/A
Device-Biologic	6	50%
Drug-Device-Biologic	2	50%
Total	30	63%

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	18	78%
CBER	3	33%
CDRH	9	44%
Total	30	63%

[12] On April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit issued a decision in *Genus Med. Techs., LLC v. FDA*, 994 F.3d 631 (D.C. Cir. 2021), holding that FDA cannot classify as a *drug* any product that meets the *device* definition in section 201(h) of the Federal Food, Drug, and Cosmetic Act. A *Federal Register* notice about this decision, issued in August 2021, is available at https://www.federalregister.gov/public-inspection/2021-16944/request-for-information-genus-medical-technologies-llc-versus-food-and-drug-administration.

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

Classification	Assignments Issued	Percent Issued in 60 Days
Drug	6	16%
Biologic	0	N/A
Device	9	78%
Total	15	53%

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	6	17%
CBER	0	N/A
CDRH	9	78%
Total	15	53%

B. OCP's Performance on Internal Center- or Office-Requested Product Classification 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 FDA's Centers/Offices (i.e., Classification and Center-Assignment Consultations (CCA Consults)). 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 2019 to FY 2021.

Center Assignment	FY 19	FY 20	FY 21
CDER	51	44	35
CBER	4	4	8
CDRH	14	27	23
Unassigned*	4	4	33[13]
Total	73	79	99

* 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 or if the product is not regulated by a human medical product Center.

Table 12 details additional OCP activities related to product classification and Center assignment that do not fall within the classification and assignment activities reported above. These additional activities include responding to email queries regarding the Pre-RFD and/or RFD processes, providing feedback to sponsors regarding the design of their studies to evaluate the PMOA of a combination product, and/or holding informational meetings/teleconferences with sponsors that plan to submit RFD or Pre-RFD submissions.

Table 12. Number of OCP's Additional Product Classification and Center-Assignment Activities from FY 2019 to FY 2021.

	FY 19	FY 20[14]	FY 21
Jurisdiction/Classification Activities[15]	463	950	375

[13] Prior to FY 2021, CCA consults that were determined to be unassigned—due to the sponsor being referred to OCP to request product classification or Center-assignment feedback via a Pre-RFD or RFD—were captured as an additional activity, as can be seen in Table 12. Due to system enhancements in FY 2021, OCP now shows these as unassigned CCA consults in Table 11.

[14] There was not an obvious cause for the increase in additional product classification and Center-assignment activities in FY 2020.

[15] Within FY 2021, OCP enhanced its ability to track inquiries and other activities by launching a technical solution, which will likely enable a more granular assessment of the queries received and the ability to identify topics that may warrant more guidance.

C. OCP's FY 2021 Activities and Accomplishments

Table 13 highlights OCP's Activities for classification and Center-assignment for FY 2021.

Table 13. Specific FY 2021 Activities by OCP.

Type of Activity	FY 2021 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-labeled combination product classification and assignment, (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.

III. 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").[16] 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 2021, FDA continued its efforts to improve the inter-Center consult process for combination products, including completing significant updates 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 surveys and direct user interactions. 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, which ultimately ensures an efficient review process and promotes alignment of Agency efforts. 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).

A. 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 2021 by CBER, CDER, and CDRH (including submissions filed or received in FY 2021), 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

[16] See https://www.fda.gov/media/81927/download.

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.

B. Requirement Workload Trends: FY 2016 to FY 2021

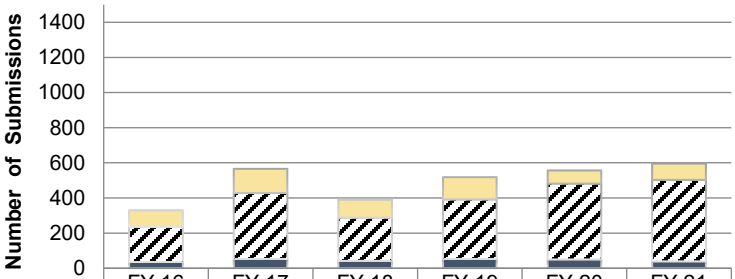
As shown in Table 14, 596 original applications were submitted for review in FY 2021.

Table 14. FY 2016 to FY 2021 Submission Review Workloads.

Submission/ Request	FY 16	FY 17	FY 18	FY 19	FY 20	FY 21
Total Combination Products Submitted for Review	330	566	390	518	557	596

As reflected in Table 15, of all original combination product applications, 78 percent were received by CDER, 16 percent were received by CDRH, and 7 percent were received by CBER.

Table 15. Combination Product Original Applications Submitted, by Center.



	FY 16	FY 17	FY 18	FY 19	FY 20	FY 21
Total	330	566	390	518	557	596
CDRH	95	138	102	126	75	93
CDER	199	375	246	339	432	464
CBER	36	53	42	53	50	39

Table 16 presents the 596 original applications for combination products received in FY 2021, broken down by the identified 10 application types and by the product's initial classification into one of nine categories of combination products.[17] The same table reflecting applications received in FY 2020 has been updated in Appendix A to reflect corrections and actions as of September 30, 2021. The majority of the applications received in FY 2021 were original investigational new drug applications (INDs) (53 percent), followed by ANDAs (21 percent). Also, the most common combination product category was the pre-filled drug delivery device/system (28 percent).

[17] 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).

Table 16. Workload by Combination Product Category Number.

Application Type	1	2	3	4	5	6	7	8	9	Total
Original NDA	13	24	0	1	0	0	0	0	3	41
Original BLA	1	0	11	0	0	0	0	0	2	14
Original PMA	0	0	0	4	0	0	0	0	0	4
Original 510(k)	5	0	1	39	0	0	1	0	0	46
Original IND	14	63	51	4	4	43	9	116	11	315
Original Investigational Device Exemption (IDE)	1	0	0	24	13	0	5	2	6	51
Original Humanitarian Device Exemption (HDE)	0	0	0	0	0	0	0	0	0	0
Original ANDA	34	81	0	0	0	0	0	0	8	123
Biosimilar BLA	0	0	0	0	0	0	0	0	0	0
De Novo	0	0	0	2	0	0	0	0	0	2
Total	68	168	63	74	17	43	15	118	30	596

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

1. 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. Unlike submission data, these data reflect consultations relating to original applications and supplements to combination product applications, as well as consultations relating to postmarket oversight for combination products. Consultations between Centers are expected during FDA's premarket review of most combination products; these consultations help ensure that relevant FDA expertise, as well as consistency in FDA's regulatory practice, is applied to each review.

There can be, for example, multiple consults for a single combination product submission or, alternatively, a submission may not warrant a consult because (1) the relevant expertise resides in the lead Center and (2) a 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; other CDRH consult topics include human factors and software.[18]

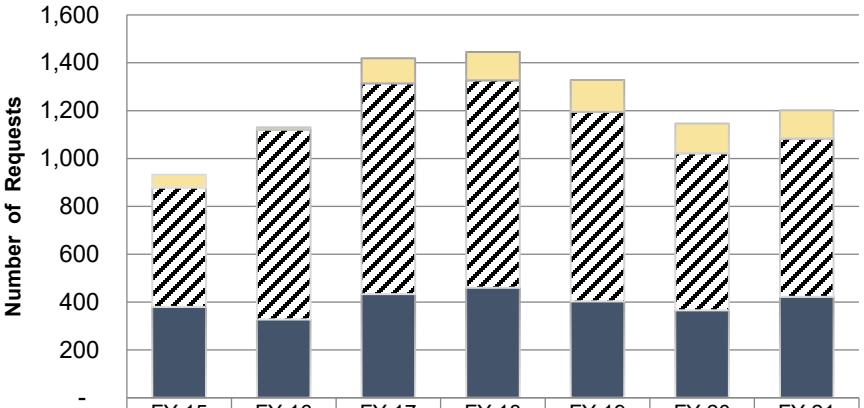
OCP oversees and facilitates coordination among review Centers under the inter-Center consult process to ensure consults are completed in a timely manner. For example, OCP monitors ongoing inter-Center consult requests for correctness (e.g., ensuring the information in the consult requests are complete and confirming the requests are being directed to the correct recipient) and timeliness (e.g., ensuring that consults allow the recipient adequate time to complete the request while accounting for the established product review goals); clarifies internal operating procedures, roles, and responsibilities related to the inter-Center consult process; helps identify consulting divisions and contacts; facilitates consultant access to review documents; and manages help desks. 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 works with CBER, CDER, and CDRH in identifying potential areas of improvement and implementing changes to improve the consult process. An efficient and effective inter-Center consult request process helps Centers meet their user fee performance commitments and promotes alignment of Agency efforts, all of which ultimately helps bring new treatment options to patients sooner.

In FY 2021, there were 1,202 inter-Center consults for combination products. Table 17 shows the number of FY 2021 inter-Center consults requested by each of the three human medical product Centers.

[18] Of note, there are other inter-Center consults that may not directly involve combination products. For example, consults regarding the use of companion diagnostics with drug or biological products that do not comprise a combination product, investigational studies of a non-combination product that involve another Center's products or expertise, requests for clinical expertise that may not be available in a particular Center, and communications between Centers to determine whether postmarket safety events or signals regarding a noncombination product warrant further investigation. Furthermore, cross-Center collaboration 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 (see http://www.fda.gov/media/81927/download).

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



	FY 15	FY 16	FY 17	FY 18	FY 19	FY 20	FY 21
Total	932	1,130	1,419	1,445	1,328	1,146	1,202
CBER	53	9	105	118	133	124	119
CDER	499	793	881	867	792	656	661
CDRH	380	328	433	460	403	366	422

In Table 18, the total number of inter-Center consults in FY 2021 is compared to the previous 5 years.

Table 18. FY 2016 to FY 2021 Inter-Center Consult Workloads.

Submission/Request	FY 16	FY 17	FY 18	FY 19	FY 20	FY 21
Total Inter-Center Consult Requests	1,130	1,419	1,445	1,328	1,146	1,202

In Table 19, the number of inter-Center consult requests during FY 2021 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	CVM*	OC	Number of Consults
CBER	--	22	96	1	--	119
CDER	11	--	650	--	--	661
CDRH	5	415	--	--	2	422
Total	16	437	746	1	2	1,202

* In addition to consultations to CBER, CDER, and CDRH, the Center for Veterinary Medicine (CVM) may be consulted either (1) when a unique aspect of a product's indication, formulation, design, or performance raises concerns that require review by another Center or (2) when the expertise to review a particular aspect of the product resides in another Center. The inclusion of CVM in the inter-Center consult process, when appropriate, ensures a comprehensive review of the product.

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	--	71	--	71
BLA	6	110	--	116
IND/Pre-IND	99	348	--	447
NDA	--	128	--	128
510(k)	--	--	2	2
De Novo	--	--	17	17
IDE	7	--	86	93
PMA		--	135	135
Pre-Submission	6	--	178	184
Other**	1	4	4	9
Total	119	661	422	1,202

* Inter-Center consult counts include consults for supplements, amendments, etc. to a marketing authorization, not just for original submissions.
** For example, an inter-Center consult related to an Emergency Use Authorization may fall in this "Other" category.

C. 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. 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 timeframe. 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 Goal 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 2020 and FY 2021 Review Performance Results," updates FDA's final review performance results on the FY 2020 combination product submissions and presents FDA's preliminary[19] review performance results on the FY 2021 combination product submissions through September 30, 2021.

D. FY 2020 and FY 2021 Review Performance Results

Table 22 shows the final FY 2020 review goal performance results.

[19] *Preliminary* means that the numbers are based on final decisions at the time of the data run and might change.

Table 22. Final FY 2020 Review Goal Performance Results.

Original Application Type	Review Type	Review Goal Within	Number of Combination Products	Median or Actual Review Time (Days)	Range of Review Time (Days)
NDAs	Priority	6 Months	9	238	59 to 456
NDAs	Standard	10 Months	16	304	60 to 388
BLAs	Priority	6 Months	1	214	214
BLAs	Standard	10 Months	2	364	285 to 426
Biosimilar BLAs	Standard	10 Months	1	361	361
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
ANDAs	Standard	10 Months	70	300	283 to 466
ANDAs	Priority without Pre-Submission Facility Correspondence	10 Months	13	302	268 to 430
ANDAs	Priority with Pre-Submission Facility Correspondence	8 Months	5	238	230 to 240
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.

Table 23 shows preliminary FY 2021 review goal performance results through September 30, 2021.

Table 23. Preliminary FY 2021 Review Goal Performance Results.

Original Application Type	Review Type	Review Goal Within	Number of Combination Products	Median or Actual Review Time (Days)	Range of Review Time (Days)
NDAs	Priority	6 Months	12	182	150 to 245
NDAs	Standard	10 Months	25	302	6 to 393
BLAs	Priority	6 Months	3	224	182 to 245
BLAs	Standard	10 Months	5	364	336 to 456
Biosimilar BLAs	Standard	10 Months	0	N/A	N/A
Expedited and Original PMAs	Standard	180 or 320 Days	3	180	112 to 180
510(k)s	Standard	90 Days	26	86	0 to 230
ANDAs	Standard	10 Months	65	301	275 to 491
ANDAs	Priority without Pre-Submission Facility Correspondence	10 Months	28	300	219 to 464
ANDAs	Priority with Pre-Submission Facility Correspondence	8 Months	5	239	217 to 337
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.

1. Premarket Review Facilitation/Oversight

OCP continues to facilitate the premarket review of combination products that raise complex regulatory issues, scientific/technical concerns, 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's 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 on the appropriate use and interpretation of

combination product categorization for premarket submissions and in determining the correct combination product categories for data reporting purposes. In addition, OCP leads or participates in product-specific meetings and discussions (1) to ensure efficient and effective communications between sponsors and FDA's review staff and between FDA's review staff, (2) to align data expectations for products raising similar regulatory questions, and (3) to respond to regulatory questions related to combination products.

The number of OCP's product-specific documented premarket review actions from FY 2016 to FY 2021 are presented in Table 24. In particular, in FY 2021, OCP received 124 requests for product-specific assistance, the responses to which contributed to ensuring the timely, effective, and aligned review of combination products.[20]

Table 24. Number of OCP's Documented Premarket Activities from FY 2016 to FY 2021.

	FY 16	FY 17	FY 18	FY 19	FY 20	FY 21
Premarket Review Activities	266	525	321	144	188	124

Notably, in FY 2021, OCP addressed issues including the following:

- 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;
- 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

[20] 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.

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

In addition to addressing these issues, OCP completed the following premarket activities during FY 2021:

- For SARS-CoV-2- or COVID-19-related product development, OCP provided rapid support to the Centers in developing responses to sponsors about the classification and Center assignment of their applicable product and provided guidance to the sponsors relevant to their product. OCP participated in developing a template to facilitate FDA's review of its responses to industry for COVID-19 submissions for over-the-counter and prescription combination products.

- OCP facilitated the resolution of master file review communication uncertainties and led an inter-Center working group to align the Agency master file processes.

- OCP hosted premarket meetings with industry and Agency subject-matter experts to provide clarifications on the use of master files for specific combination products.

- OCP assisted 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 are presented in Table 25.

Table 25. Other Significant Premarket Review Facilitation or Assistance Provided by OCP in FY 2021.

Type of Activity	FY 2021 Accomplishments
Providing Significant Premarket Review Facilitation or Assistance	With respect to the following specific products or categories of products, and other premarket regulatory issues, OCP provided significant assistance with: • Novel drug-device cancer therapies or treatment selection technologies; • Injector delivery systems (e.g., intrathecal infusion systems); • Facilitation of premarket current good manufacturing practice (CGMP)/21 CFR part 4 compliance assessments; • Clarification of the IND human factors protocol submission process and the review of these study results; • Implication of packaging changes during product development; • Alignment of IND and IDE review requirements for combination products; • Consideration of the suitability of a single combination product application or separate submissions for each constituent part; • Facilitation of FDA's human factors review timeliness considerations; • Facilitation of resolution of issues raised by use of data previously in a closed master file; • Facilitation of consistent reviews of on-body wearable injection or infusion systems; • Review considerations for combination products that include software for monitoring, treatment dose adjustment, or product ordering; • Considerations for drug-device interactions in implants; • Facilitation of interactive dialogue between the review team and the application holder to address deficiencies identified by cross-Center consultants; • Facilitation of FDA's resolution of informal premarket timeliness concerns; • Facilitation of FDA's resolution of review process concerns raised by novel bone void filler; and • Implementation testing of the new electronic common technical document database for premarket review of submissions in CDER and CBER.

IV. Combination Product Postmarket Activities

The Center to which a combination product is assigned for premarket review has primary jurisdiction for the regulation of the combination product, including for ensuring compliance with postmarketing regulatory requirements and performing postmarket surveillance. 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.

The right balance of premarket and postmarket oversight activities can facilitate timely patient access to safe and effective products. Consistent and appropriate postmarketing regulatory requirements help the Agency prevent, detect, and respond quickly to a product safety or product quality problem, which minimizes the risk of patients encountering such problems. Postmarket inspection and other activities for the appropriate control of manufacturing procedures is one important element to ensure marketed products remain safe and effective. Postmarket surveillance activities are also critical to protect patients from risks associated with products currently on the market. Combination products pose particular challenges due to their complexity and the range of scientific, technical, and regulatory issues that can arise.

OCP undertakes a variety of compliance-related and postmarket oversight activities to help ensure the safety and quality of combination products. These activities include leading the Agency's efforts to develop and publish regulations, guidance documents, 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, 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 2021 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 2016 to FY 2021.

	FY 16	FY 17	FY 18	FY 19	FY 20	FY 21
Postmarket Regulatory Activities	50	74	86	62	113	84

OCP engaged in 84 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.[21] 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 combination product CGMP requirements and inspectional approaches (see also the discussion of a final compliance program under the "Policy Activities and Accomplishments" section below); and

- Continuing to facilitate the implementation of the PMSR final rule[22] for combination products' requirements (through analyzing data, training staff, and enhancing a technical tool for postmarket staff).

[21] 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 (http://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.

[22] See 81 FR 92603 (Dec. 20, 2016), available at https://www.federalregister.gov/documents/2016/12/20/2016-30485/postmarketing-safety-reporting-for-combination-products

V. 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).

A. 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 2021. 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). Data provided in the "Premarket Review Facilitation/Oversight" section of this report provide examples of OCP's informal facilitation and resolution of issues related to premarket review.

VI. Policy Activities and Accomplishments

OCP's policy activities include leading and contributing to policy initiatives important to the regulation of combination products. Key examples of such activities pursued in FY 2021 are discussed below and included in the tables to follow.

A. Supporting and Implementing Legislative Initiatives

OCP participated in the development of FDA's positions in response to congressional inquiries and in the development of legislative proposals. Furthermore, OCP continued its efforts, in coordination with the human medical product Centers, to implement section 3038 of the Cures Act regarding combination products. Activities in this regard included the following: issuing regulations and guidance documents, enhancing standard operating procedures, developing improvements to IT systems, training staff, and conducting outreach to stakeholders. In addition, OCP was involved in implementing PDUFA VI activities related to combination products (e.g., developing bridging and human factors guidance documents).

B. Streamlining Regulation

OCP continued its work on amending FDA's jurisdictional regulations in 21 CFR part 3, including considering comments received on the proposed rule,[23] to update and clarify the regulations in light of legislative and other policy developments. OCP also supported rulemakings relating to combination products led by the human medical product Centers, including rulemakings on the use of the De Novo classification process for devices and combination products and an amendment of device quality system regulations and associated adjustments to CGMP requirements for combination products under 21 CFR part 4.

C. Clarifying Regulatory Policy

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

OCP led the development and publication of the following documents:

- Final guidance document on requesting FDA's feedback on combination products (December 2020)[24]

[23] See 83 FR 22428 (May 15, 2018), available at http://www.federalregister.gov/documents/2018/05/15/2018-10321/product-jurisdiction.

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

- *Federal Register* notice announcing the Agency's consolidation of devices that process autologous human cells, tissues, and cellular and tissue-based products at the point of care to produce a therapeutic article (September 2021)[25]

OCP contributed to the development and publication of the following documents:

- Final guidance document on requests for feedback and meetings for medical device submissions in the Q-Submission Program (January 2021)[26]

- Final guidance document on manufacturing considerations for licensed and investigational cellular and gene therapy products during the COVID-19 public health emergency (January 2021)[27]

- Draft guidance document on considerations for the implementation of the International Council for Harmonisation's (ICH's) Q12 guiding principles with respect to FDA-regulated products (May 2021)[28]

- Final guidance document providing a harmonized approach regarding Q12 technical and regulatory considerations for pharmaceutical product lifecycle management (May 2021)[29]

- Final guidance document providing questions and answers on field alert report submissions (July 2021)[30]

    - *Federal Register* notice regarding *Genus Med. Techs., LLC v. FDA*, 994 F.3d 631 (D.C. Cir. 2021) (August 2021)[31]

    - Final rule on importation of prescription drugs (October 2020)[32]

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[25] 86 FR 50887 (Sept. 13, 2021), available at http://www.federalregister.gov/documents/2021/09/13/2021-18912/consolidation-of-devices-that-process-autologous-human-cells-tissues-and-cellular-and-tissue-based.

[26]Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program

[27] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/manufacturing-considerations-licensed-and-investigational-cellular-and-gene-therapy-products-during.

[28] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ich-q12-implementation-considerations-fda-regulated-products.

[29] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q12-technical-and-regulatory-considerations-pharmaceutical-product-lifecycle-management-guidance.

[30] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/field-alert-report-submission-questions-and-answers-guidance-industry.

[31] 86 FR 43553 (Aug. 9, 2021), available at https://www.federalregister.gov/documents/2021/08/09/2021-16944/genus-medical-technologies-llc-versus-food-and-drug-administration-request-for-information-and.

[32] Available at https://www.federalregister.gov/documents/2020/10/01/2020-21522/importation-of-prescription-drugs.

- Final guidance document on importation of certain FDA-approved human prescription drugs, including biological products and combination products, under section 801(d)(1)(B) of the Federal Food, Drug, and Cosmetic Act (October 2020)[33]

D. Other Policy-Related Activities

Additional policy-related activities included the following:

- Enhanced 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 performance evaluations and updates of procedural and IT systems to enable the implementation of the final PMSR rule for combination products;

- Continued developing and training on the PMSR requirements to FDA's human medical product Centers' product safety offices and other staff involved with addressing safety signals; and

- Providing training and reference information on the compliance program for combination product CGMPs to inspectors in the Office of Regulatory Affairs' medical product programs and to human medical product Center staff involved with manufacturing and compliance activities.

Tables 27 through 29 identify FDA's policy development work that continued in FY 2022; this work is categorized by topic area (i.e., jurisdiction, premarket review, postmarket regulation) and activity type.

[33] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/importation-certain-fda-approved-human-prescription-drugs-including-biological-products-and.

Table 27. Additional Jurisdictional Regulatory Initiatives.

Type of Activity	FY 2021 Activities
Developing regulations and guidance documents	OCP's jurisdiction-related activities included participating in the following Agency rulemaking and guidance initiatives: • Led a cross-Center working group on the scope and significance of the status of cross-labeled combination products • Led updates to the guidance on preparation of RFDs and Pre-RFDs
Participating in other inter-Center and Agency-wide working groups to clarify issues related to product jurisdiction	OCP's jurisdiction-related activities included the following: • Continued to enhance the efficiency and transparency of the RFD and Pre-RFD programs • Developed standard operating procedures to facilitate product classification

Table 28. Additional Premarket Review Regulatory Initiatives.

Type of Activity	FY 2021 Activities
Developing regulations, guidance documents, and other policy documents	OCP's premarket review-related activities included leading the following Agency guidance and other policy initiatives: • Continued to lead the development of a guidance document on human factors studies for combination products. • Continued to chair a cross-Center working group and lead the development of a draft guidance document for the technical aspects of intravaginal system combination products. • Led the development of a final guidance document on the technical considerations for demonstrating the reliability of combination product emergency-use injectors. • Continued to lead a cross-Center working group to develop a guidance document on essential performance requirements.

Type of Activity	FY 2021 Activities

	• Continued to work with Centers to assess approaches for insulin pump labeling considerations.
	• Led efforts to:
	  ○ Finalize a guidance document on premarket principles and pathways for combination products.
	  ○ Update a guidance document on the application of user fees for combination products.
	  ○ Revise the published draft guidance document on postmarket changes for combination products.
	  ○ Revise inter-Center agreements on medical product Center assignment/regulatory 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
	• Cross-Center draft guidance document on technical considerations for the visual inspection of particulates in injectable solutions
	• Cross-Center draft guidance document on considerations for what constitutes clinical data for user fee purposes
	• Cross-Center draft guidance document on 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 13485 and associated amendments to part 4
	• ICH's Q12 implementation guidance document

Assessing regulatory pathways for new products intended to be	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

Type of Activity	FY 2021 Activities
used with another sponsor's already approved product	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 following: • Non-prescription drug availability • The Agency's thinking on the regulation of certain software output as drug labeling • Application of artificial intelligence and machine learning in investigational, diagnostic and treatment settings • 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 developments and enhancements. • OCP continued to chair a cross-Center working group to develop procedures to create standardization and efficiency in the management of master files that will be used by more than one Center.

Table 29. Additional Postmarket Review Regulatory Initiatives.

Type of Activity	FY 2021 Activities
Leading or participating in other Inter-Center and Agency-wide working groups to clarify issues related to combination products	OCP's postmarket review-related activities included participating in the following initiatives: • OCP continued to chair working groups relating to the PMSR requirements for combination products. This work focused on implementation of the rule, monitoring engagement between the Centers and OCP on postmarket combination product issues, and developing and delivering internal training. • OCP continued leading activities to support implementation of CGMP requirements for combination products, training inspectional and compliance staff, and finalizing a *Federal Register* notice on CGMP alternatives/flexibilities. • OCP continued to work with Centers on track and trace programs with respect to combination products, including a guidance document on the use of unique device identifiers, numeric drug codes, 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 to work on best manufacturing practices, training of regulated entities' staff on combination product regulation, and best practices across the combination products' lifecycle. • OCP continued to participate in an ASTM International standard setting process to clarify terminology related to combination products and the combined use of different types of medical products.

VIII. Additional Activities and Accomplishments

A. 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 2021 to improve the Inter-Center Consult Request workflow and data capture system, including changes to better enable the requesting Center to know to which group they should send a consult request.

- OCP implemented 11 enhancement releases in FY 2021 to improve the PMSR dashboard functionality and user experience. This tool, to the extent feasible, integrates data on combination products from different data sources—such as premarket systems, registration and listing systems, and adverse event reporting systems—from all three human medical product Centers into a single point of reference to enhance the efficiency and consistency of postmarket safety activities. These enhancement releases included adding a new data source, automating the connection to several existing data sources, and reorganizing and adding content based on user feedback.

- OCP continued to improve the electronic system that manages the workflow and data capture for Pre-RFDs and RFDs. OCP continued the 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. OCP also engaged users through surveys, focus groups, direct interactions, and other means to solicit feedback and identify potential improvements to the IT systems.

B. External Outreach

OCP engages 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) that represent the drug, device, biological product, and combination product industries; OCP engages them on FDA's classification, assignment, and regulation of combination products and related regulatory topics. These engagement efforts enhance two-way communication between the Agency and external stakeholders and help address questions or challenges faced by sponsors developing combination products. 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 the International

Organization for Standardization, ICH, International Medical Device Regulators Forum, and ASTM International. OCP also presented at various industry conferences. These conferences offered opportunities for Agency officials to engage with stakeholders, to clarify areas of stakeholder confusion, and to learn about stakeholder questions and concerns that may warrant investigation and, if needed, the development of policy by FDA to address those concerns.

In FY 2021, FDA addressed a wide range of topics about which stakeholders had questions, concerns, or proposals for Agency consideration. These topics included emerging issues in combination product regulation and the broader area of combined use of separately distributed medical products; opportunities for regulatory convergence across jurisdictions; the role of OCP; policies and guidance documents under development; rulemakings; regulatory issues for specific categories of combination products, particularly cross-cutting regulatory issues for combination products and combined use products; and stakeholder priorities for further action.

Examples of OCP's FY 2021 outreach activities via industry conferences are included in Table 30.

Table 30. Examples of FY 2021 Outreach Activities.

Type of Activity	FY 2021 Accomplishments
Presentations and outreach activities	The following are examples of venues/events for which OCP provided presentations and/or educational outreach: • Drug Information Association's Combination Products Conference (October 2020) • Xavier University Health's Combination Products Summit (October 2020) • Drug Information Association's and FDA's "Workshop on complex generic drug-device combination products" – Steering Committee to develop the October 2020 workshop • Medtech's Summit: Virtual Medical Device Summit (October 2020) • 2020 PDA Combination Products Workshop (October 2020) • 3rd Annual Lifecycle Management for Combination Products (November 2020) • Xavier University Health's Combination Products Summit (September 2021) • The Organisation for Professionals in Regulatory Affairs' Annual Symposium (September 2021) • Global Bio Conference, South Korean Ministry of Food and Drug Safety (September 2021)

Appendix A: FY 2020 Updated Performance Detail

The table below reflects the 557 original applications classified into one of nine categories of combination products received in FY 2020.

Table 1. Workload by Combination Product Category Number.

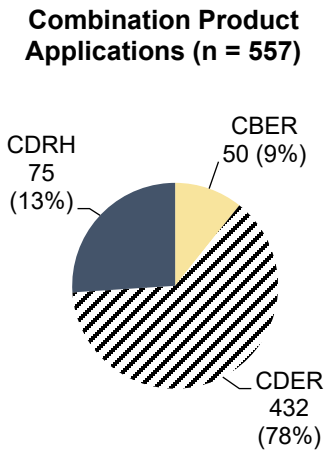
Application Type	1	2	3	4	5	6	7	8	9	Total
Original NDA	12	11	0	0	0	0	0	0	3	26
Original BLA	2	0	12	0	0	1	0	0	1	16
Original PMA	1	0	0	0	0	0	0	0	0	1
Original 510(k)	4	0	0	29	1	0	2	2	0	38
Original IND	27	38	54	6	8	85	3	96	26	343
Original IDE	0	0	0	16	9	0	7	5	7	44
Original HDE	0	0	0	0	0	0	0	0	0	0
Original ANDA	20	69	0	0	0	0	0	0	0	89
Biosimilar BLA	0	0	0	0	0	0	0	0	0	0
De Novo	0	0	0	0	0	0	0	0	0	0
Total	66	118	66	51	18	86	12	103	37	557

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 2020 by Center lead, as of September 30, 2021.



This report was prepared by FDA's Office of Combination Products in collaboration with the Office of Planning, Evaluation, and Risk Management in the Office of the Commissioner, the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and the Center for Devices and Radiological Health. For further information please contact:

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