Performance Report to Congress

Office of Combination Products

FY 2024

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

U.S. FOOD & DRUG ADMINISTRATION

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) 2024 (i.e., October 1, 2023, to September 30, 2024). This report highlights the following OCP activities for FY 2024:

A. Prompt Assignment of Combination Products

Sponsors may submit Requests for Designation (RFDs) 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 2024, OCP issued five combination product and six non-combination product RFD decisions, with every classification and/or assignment decision meeting FDA's 60-day statutory requirement. Alternatively, sponsors 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 2024, OCP provided classification and Center assignment feedback for 39 Pre-RFDs. (For more information, see the "Policy and Procedural Activities and Accomplishments" section below.)

B. Timely, Effective, and Aligned Combination Product Premarket Review

In FY 2024, OCP conducted several activities related to the premarket review of combination products. For instance, OCP received 270 requests for product-specific premarket assistance, the responses to which contributed to ensuring FDA's timely, effective, and aligned review of combination products. OCP'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 several inter-Center working groups to examine complex

[1] Examples of combination product types can be found on the Combination Products website, which is available at https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types.

regulatory issues, clarify regulatory standards, address challenging categories of products, improve the premarket review process, and address developmental considerations for combination products. Further, in FY 2024, FDA received 645 original premarket applications for combination products. There were 1,162 inter-Center consulting reviews for combination products in FY 2024. (For more information, see the "Policy and Procedural Activities and Accomplishments" section below.)

C. Consistent and Appropriate Postmarket Regulation

In FY 2024, OCP provided clarification and support for 38 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 2024, OCP continued to implement section 3038 of the 21st Century Cures Act, which focuses on enhancing the clarity, predictability, efficiency, and consistency of premarket regulatory expectations for combination products, including by ensuring that the Agency's components and staff coordinate appropriately on the premarket review of these products and that the Agency's thinking is aligned in conducting these reviews. Furthermore, OCP continued to develop policy regarding complex regulatory and procedural questions for combination products. OCP also continued to develop policy related to the classification and assignment of challenging medical products.

For example, OCP published the guidance document, Essential Drug Delivery Outputs (EDDO) for Devices Intended to Deliver Drugs and Biological Products.[2] Also, OCP continued to issue system updates and provide training to enhance the efficiency of the inter-Center consult process, the RFD/Pre-RFD review and decision process, and the combination product PMSR dashboard.

OCP also continued, in FY 2024, to conduct external outreach activities through engagement with interested parties 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

[2] Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/essential-drug-delivery-outputs-devices-intended-deliver-drugs-and-biological-products

settings for combination products; clarify how interested parties can engage with FDA on these issues; enable FDA to understand and respond to questions and concerns from interested parties; and identify potential areas for regulatory convergence across jurisdictions for FDA's oversight of combination products.

Table of Contents

Acronym List

510(k)	Premarket Notification
ANDA	Abbreviated New Drug Application
ASTM	American Society for Testing and Materials
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 of Technical Requirements for Pharmaceuticals for Human Use
IDE	Investigational Device Exemption
IND	Investigational New Drug
IT	Information Technology
MDUFA	Medical Device User Fee Amendments
MDUFMA	Medical Device User Fee and Modernization Act of 2002
NDA	New Drug Application
OCC	Office of the Chief Counsel
OCP	Office of Combination Products
PDUFA	Prescription Drug User Fee Act
PMA	Premarket Approval Application

PMOA	Primary Mode of Action
PMSR	Postmarketing Safety Reporting
Pre-RFD	Pre-Request for Designation
RFD	Request for Designation
SMG	Staff Manual Guide

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 subject to the same statutory requirements 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 incorporated into the Federal Food, Drug, and Cosmetic Act, and amended by the Cures Act, can be found on the Combination Products website.[3]

A. Description of Combination Products

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

(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

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

specified 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[4] (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, biologic-device combinations, 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.[5] 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;

[4] Throughout this document, the terms "medical product" and "human medical product" may be used interchangeably, and they refer to human drugs, devices, biological products, and/or combination 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.

[5] 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 2024 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 interested parties 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." Sponsors may submit RFDs to 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. OCP's determinations regarding such classifications and/or Center assignments are binding and 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 2024 activities and accomplishments, including its fulfillment of statutory mandates. This report presents information and data on OCP's activities related to the following:[6]

- Prompt assignment of combination products
    - Timeliness of the classification and assignment of combination products
- Timely and effective premarket review

[6] FDA has initiated various activities related to its implementation of the Cures Act's requirements for combination products, and this report provides new information relating to the Cures Act's requirements and provisions. As implementation of the Cures Act proceeds, the Agency will consider what additional information or adjustments may be appropriate for subsequent reports.

See 21 USC 353 available at

https://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title21-section353&num=0&edition=prelim

    - 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

    - 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, 2024.

II. Prompt Assignment of Combination Products

Sponsors may submit RFD submissions to obtain formal Agency determinations from OCP 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 (i.e., CBER, CDER, or CDRH) for the product's premarket review and regulation.

For combination products, OCP generally 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's 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.[7] Further, OCP leads and/or supports other Agency efforts to develop and publish regulations, guidance documents, and procedures 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. 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 the information needed by OCP to determine 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 2020 to FY 2024

OCP received 48 RFD submissions in FY 2024. Of the 48 total RFD submissions that were received and reviewed in FY 2024, nine RFD submissions (19%)[8] had a decision issued, 34 RFD submissions (71%) were found to have insufficient information for filing,

[7] 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."

[8] All percent values are rounded to the nearest whole number for this entire report.

and five RFD submissions (10%) were withdrawn[9] by the sponsor. Two RFD submissions received in FY 2023 were completed in FY 2024[10]. Of the 11 RFD determinations made in FY 2024, five were classified as combination products and six were classified as non-combination products.

In Table 1, the total number of RFD determinations (i.e., classifications and assignments for both combination and non-combination products) in FY 2024 is compared to the previous 4 years.

Table 1. RFD Determinations from FY 2020 to FY 2024.

RFD Submissions	FY 20	FY 21	FY 22	FY 23	FY 24
Total RFD Combination Product Classifications/ Assignments	7	1	2	4	5
Total RFD Non-Combination Product Classifications/ Assignments	2	2	2	4	6

In FY 2024, the 11 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 60 days. Four RFD determinations classified the products as device-drug combination products. One RFD determination classified the product as a device-drug-biologic combination product. Six RFD determinations classified the products as non-combination products: Four were drugs, and the other two were biological products.

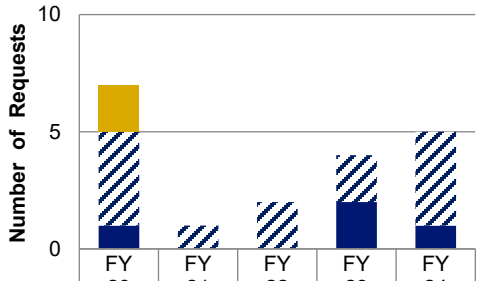
[9] For withdrawn RFD/Pre-RFDs, some were withdrawn at the request of sponsors after informal feedback was given during filing which determined that a submission was not required. In other cases, submissions were made in error, and withdrawal was requested by the sponsors.

[10] Two of the 11 RFD determinations made in FY 2024, were received at the end of FY 2023 with a filing decision due date in FY 2024.

As shown in Table 2, the total number of RFD combination product Center assignment determinations in FY 2024 increased by one from FY 2023.

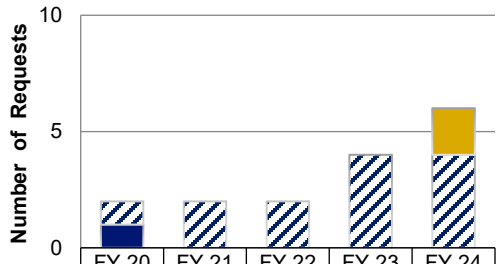
As shown in Table 3, the total number of RFD non-combination product Center assignment determinations in FY 2024 increased by two from FY 2023.

Table 2. Combination Product Assignment Determinations.



	FY 20	FY 21	FY 22	FY 23	FY 24
Total	7	1	2	4	5
CBER	2	0	0	0	0
CDER	4	1	2	2	4
CDRH	1	0	0	2	1

Table 3. Non-Combination Product Assignment Determinations.



	FY 20	FY 21	FY 22	FY 23	FY 24
Total	2	2	2	4	6
CBER	0	0	0	0	2
CDER	1	2	2	4	4
CDRH	1	0	0	0	0

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*
Device-Drug	4	100%
Drug-Biologic	0	NA
Device-Biologic	0	NA
Device-Drug-Biologic	1	100%
Total	**5**	**100%**

* OCP did not receive any Requests for Reconsideration per 21 CFR 3.8 or appeal requests per 21 CFR 10.75 related to these determinations for FY 2024.

Table 5. Timeliness of Non-Combination Product Determinations.

Determination	Product Assignments Issued^	Percent On Time^
Drug	4	100%
Biologic	2	100%
Device	0	NA
Total	**6**	**100%**

^ OCP did receive a Request for Reconsideration per 21 CFR 3.8 or appeal request per 21 CFR 10.75 related to one of these determinations for FY 2024.

1. Pre-RFD Workload Performance Results

OCP continues the Pre-RFD program 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 interactive discussions between FDA and a sponsor if questions arise during the review. Table 6 shows OCP's Pre-RFD submission review workloads from FY 2020 to FY 2024.

Table 6. OCP's Pre-RFD Workloads from FY 2020 to FY 2024.

Pre-RFD Assessment Decisions	FY 20	FY 21	FY 22	FY 23	FY 24
Combination Product Assessments	47	30	30	31	28
Non-Combination Product Assessments	30	15	19	28	11
Unclassified Assessments*	2	1	0	1[11]	0
Total Pre-RFD Assessments	79	46	49	60	39

* 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 are not filed because they lack sufficient information for FDA to initiate an assessment. OCP received 82 Pre-RFD submissions in FY 2024. Of the 82 received, 19 Pre-RFD submissions (23%) were completed, 36 Pre-RFD submissions (44%) were reviewed and not filed due to their lack of sufficient information for OCP to complete an assessment, and 16 Pre-RFD submissions (19%) were withdrawn by the sponsor. The remaining 11 Pre-RFD submissions (13%) received in FY 2024 are under FDA's review, and their review timeline overlaps into FY 2025.[12] In FY 2024, OCP completed the review of 39 total Pre-RFDs, of which two were received in FY 2022, 18 were received in FY 2023[13] and 19 were received in FY 2024. Twenty-nine Pre-RFD assessments (74%) were issued within OCP's internally established 60-day goal date that begins when OCP receives sufficient information to review and provide the requested feedback. The average review time for Pre-RFD submissions was 61 days, with a median review time of 45 days.

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. FDA's goal is to complete Pre-RFD assessments within 60 days;

[11] The Pre-RFD submission was for an investigational combination product. Classification and Center assignment could not be determined, as it depends on the results of the investigation.

[12] The 11 Pre-RFD submissions overlapping into FY 2025 will be reported in the FY 2025 OCP Performance report.

[13] Some of these Pre-RFD submissions were also impacted by FDA's implementation of a federal appellate court's decision in *Genus Medical Technologies, LLC v. FDA, 994 F.3d 631 (D.C. Cir. 2021) and amendment to section 503 of the FD&C Act.*

however, this goal is not always achievable. For example, for Pre-RFDs that contain substantially more information than is allowable in an RFD (i.e., submitted materials are limited to 15 pages for an RFD), this 60-day goal may not be possible. FDA's achievement of goal timeframes is commensurate with available resources.

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

Classification	Pre-RFD Assessments	Percent Issued in 60 Days
Drug-Device	23	83%
Drug-Biologic	1	N/A
Device-Biologic	2	100%
Drug-Device-Biologic	2	50%
Total	28	78%

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

Center Assignment	Pre-RFD Assessments	Percent Issued in 60 Days
CDER	21	81%
CBER	1	100%
CDRH	6	67%
Total	28	78%

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

Classification	Pre-RFD Assessments	Percent Issued in 60 Days
Drug	5	80%
Biologic	2	0%
Device	4	75%
Other	0	0%
Total	11	64%

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

Center Assignment	Pre-RFD Assessments	Percent Issued in 60 Days
CDER	5	80%
CBER	3	0%
CDRH	3	100%
Other	0	0%
Total	11	64%

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 2020 to FY 2024.

Center Assignment	FY 20	FY 21	FY 22	FY 23	FY 24
CDER	44	35	35	37	29
CBER	4	8	7	4	9
CDRH	27	23	12	7	26
Unassigned*	4	33[14]	21	27	6
Total	79	99	75	75	70

* 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 2020 to FY 2024.

	FY 20[15]	FY 21	FY 22	FY 23[16]	FY 24
Jurisdiction/Classification Activities	950	375	235	147	108

[14] 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.

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

[16] There was not an obvious cause for the decrease in additional product classification and Center-assignment activities in FY 2023.

C. OCP's FY 2024 Activities and Accomplishments

Table 13 highlights OCP's Activities for classification and Center-assignment for FY 2024.

Table 13. Specific FY 2024 Activities by OCP.

Type of Activity	FY 2024 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 considering what may be appropriate for guidance	OCP continued to: • Chair a working group composed of staff from CDER, CDRH, and CBER to clarify interpretive standards and to address the classification and Center assignment for challenging categories of products, and • Pursue and support related policy initiatives, including (1) clarifying labeling considerations for medical products intended for use with each other, (2) clarifying the regulatory status of software used with a drug or biological product, (3) 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.

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").[17] 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 2024, FDA continued its efforts to improve the inter-Center consult process for combination products, including completing continuous 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. OCP continued to apply these efforts 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 or support some Agency efforts to develop and publish regulations, guidance documents, and 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 2024 by CBER, CDER, and CDRH (including submissions filed or received in FY 2024), as well as the timeliness of these reviews.

- When reporting timeliness in days for the review for CBER-led or CDER-led

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

combination products, the Prescription Drug User Fee Act Reauthorization of 2022 (PDUFA VII) goals were referenced for priority and standard new drug applications (NDAs) and applicable biologics license applications (BLAs), the Generic Drug User Fee Amendments of 2022 (now GDUFA III) goals were referenced for abbreviated new drug applications (ANDAs), and the Biosimilar User Fee Amendments of 2022 (now BsUFA III) goals were referenced for the biosimilar BLAs. For CBER-led or CDRH-led combination products, Medical Device User Fee Amendments of 2022 (now MDUFA V) 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 VII goals. For MDUFA V goals, the median review times were based on the total MDUFA V decision review time. The actual review time was used when only one action was measured.

B. Requirement Workload Trends: FY 2020 to FY 2024

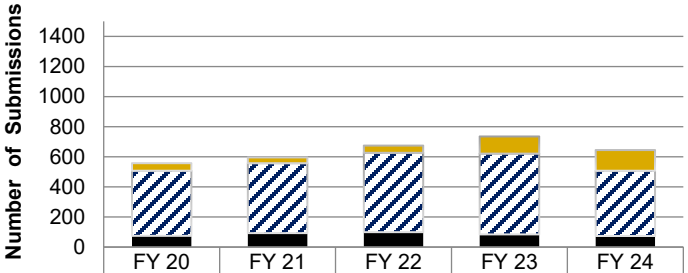
As shown in Table 14, 645 original submissions were submitted for review in FY 2024.

Table 14. FY 2020 to FY 2024 Submission Review Workloads.

Submission/Request	FY 20	FY 21	FY 22	FY 23	FY 24
Total Combination Products Submitted for Review	557	596	674	735	645

As reflected in Table 15, of the original combination product applications received, 67% were received by CDER, 11% were received by CDRH, and 21% were received by CBER. The increase in combination product applications received by CBER between FY 2022 and FY 2023 can be attributed to its updated tracking procedures.

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



	FY 20	FY 21	FY 22	FY 23	FY 24
Total	557	596	674	735	645
CBER	50	39	47	114	138
CDER	432	464	528	537	433
CDRH	75	93	99	84	74

Table 16 presents the 645 original applications for combination products received in FY 2024, broken down by the identified 10 application types and by the product's initial classification into one of nine categories of combination products.[18] The same table reflecting applications received in FY 2023 has been updated in Appendix A to reflect corrections and actions as of September 30, 2023. The majority of the applications received in FY 2024 were original investigational new drug applications (INDs) (55%), followed by ANDAs (22%). Also, the most common combination product category was the pre-filled biologic delivery device/system (26%).

[18] 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.[19]

Application Type	1	2	3	4	5	6	7	8	9	Total
Original NDA	16	11	0	0	0	1	1	0	3	32
Original BLA	1	0	33	0	1	0	1	0	1	37
Original PMA	0	0	0	6	0	0	0	0	1	7
Original 510(k)	1	0	0	33	3	0	0	1	0	38
Original IND	30	43	135	7	1	64	8	49	17	354
Original Investigational Device Exemption (IDE)	3	2	0	16	2	1	2	1	8	35
Original Humanitarian Device Exemption (HDE)	0	0	0	0	0	0	0	0	0	0
ANDA	35	101	0	0	0	0	0	0	3	139
Biosimilar BLA	0	0	0	0	0	0	0	0	0	0
De Novo	1	0	0	1	0	0	1	0	0	3
Total	87	157	168	63	7	66	13	51	33	645

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

[19] Prior to FY 2024, all IND studies with a combination product including those for single patient emergency use/compassionate use/expanded access products were reported. Starting with the FY 2024 report and future reports, single patient emergency use/compassionate use/expanded access products will no longer be reported.

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.[20]

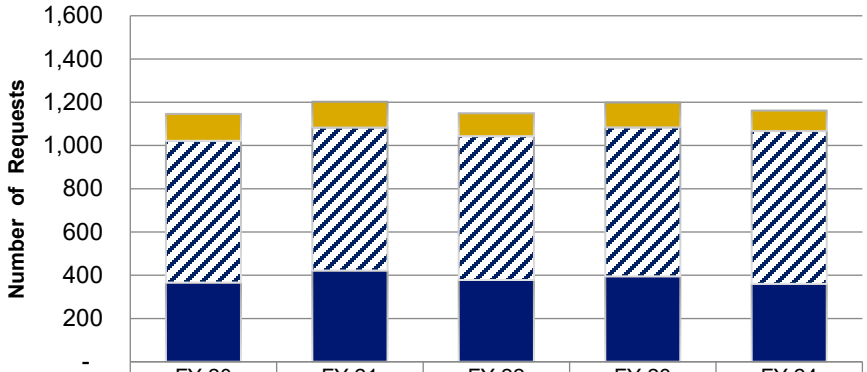
OCP oversees and facilitates coordination among review Centers under the inter-Center consult process to ensure consults are completed in a timely manner. For example, OCP monitors ongoing inter-Center consult requests for correctness (e.g., ensuring the information in the consult requests are complete 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 2024, there were 1162 inter-Center consults for combination products. Table 17 shows the number of FY 2024 inter-Center consults requested by each Center.

[20] 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 non-combination 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 for Combination Products.



	FY 20	FY 21	FY 22	FY 23	FY 24
Total	1,146	1,202	1,149	1,199	1,162
CBER	124	119	106	115	95
CDER	656	661	665	689	707
CDRH	366	422	378	395	360

In Table 18, the total number of inter-Center consults in FY 2024 is compared to the previous 5 years.

Table 18. FY 2020 to FY 2024 Inter-Center Consult Workloads for Combination Products.

Submission/Request	FY 20	FY 21	FY 22	FY 23	FY 24
Total Inter-Center Consult Requests	1,146	1,202	1,149	1,199	1,162

In Table 19, the number of inter-Center consult requests during FY 2024 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 Inter-Center Consults for Combination Products by Lead and Consulted Center.

Lead Center	Consulted Center						
	CBER	CDER	CDRH	CVM*	OC	OCE	Number of Consults
CBER	--	26	66	3	--	--	95
CDER	3	--	704	--	--	--	707
CDRH	13	346	--	--	1	--	360
Total	16	372	770	3	1	--	1,162

* 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 CVM or (2) when the expertise to review a particular aspect of the product resides in CVM. 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 during FY 2024 is broken down by application type at each Center.

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

Application Type	Lead Center			
	CBER	CDER	CDRH	Number of Consults
ANDA	--	87	--	87
BLA	10	127	--	137
IND/Pre-IND	80	356	--	436
NDA	--	132	--	132
510(k)	--	--	24	24
De Novo	--	--	8	8
IDE	--	--	99	99
PMA	--	--	92	92
Pre-Submission	1	0	135	136
Other †	4	5	2	11
Total	95	707	360	1,162

*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 VII, GDUFA III, BsUFA III, and MDUFA V established review performance goals for different types of 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% to 90% and vary by year.

- For MDUFA V performance goals, refer to https://www.fda.gov/media/157074/download
- For PDUFA VII performance goals, refer to https://www.fda.gov/media/151712/download
- For GDUFA III performance goals, refer to https://www.fda.gov/media/153631/download
- For BsUFA III performance goals, refer to https://www.fda.gov/media/152279/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
MDUFA IV	De Novos	Standard	150 Days
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

* 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).

D. FY 2023 and FY 2024 Review Performance Results

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. This section updates FDA's final review performance results on the FY 2023 combination product submissions and

presents FDA's preliminary[21] review performance results on the FY 2024 combination product submissions through September 30, 2024.

Table 22 shows the final[22] FY 2023 review goal performance results. Review goal performance data are based on the fiscal year receipt cohort.

Table 22. Final FY 2023 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)	Percent Issued Within Goal Date
NDAs	Priority	6 Months	11	236	176 to 397	82%
NDAs	Standard	10 Months	23	304	265 to 392	96%
BLAs	Priority	6 Months	6	243	182 to 322	100%
BLAs	Standard	10 Months	9	364	293 to 457	100%
Biosimilar BLAs	Standard	10 Months	13	365	361 to 458	85%
Expedited and Original PMAs	Standard	180 or 320 Days*	4	180	172 to 213	67%
510(k)s	Standard	90 Days	38	84	0 to 90	100%
De Novos	Standard	150 Days	2	75	288 to 448	100%
ANDAs	Standard	10 Months	105	306	288 to 448	100%
ANDAs	Priority without Pre-Submission Facility Correspondence	10 Months	27	382	294 to 321	100%
ANDAs	Priority with Pre-Submission Facility Correspondence	8 Months	2	240	228 to 251	100%

*These numbers include either a review within 180 days for decisions without advisory committee input or a review within 320 days for decisions with advisory committee input, respectively.

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

[22] *Final* refers to the time in which all submissions in a cohort receive a final decision or are sufficiently complete for FDA to determine whether the review goal has been met.

Table 23 shows preliminary FY 2024 review goal performance results through September 30, 2024.

Table 23. Preliminary FY 2024 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)	Percent Issued Within Goal Date
NDAs	Priority	6 Months	7	231	182 to 231	100%
NDAs	Standard	10 Months	22	304	156 to 383	96%
BLAs	Priority	6 Months	5	244	229 to 244	100%
BLAs	Standard	10 Months	18	366	302 to 456	93%
Biosimilar BLAs	Standard	10 Months	8	240	151 to 366	100%
Expedited and Original PMAs	Standard	180 or 320 Days*	2	162	147 to 178	100%
510(k)s	Standard	90 Days	28	85	28 to 90	100%
De Novos	Standard	150 Days	1	143	143	100%
ANDAs	Standard	10 Months	98	302	210 to 432	100%
ANDAs	Priority without Pre-Submission Facility Correspondence	10 Months	38	302	286 to 395	100%
ANDAs	Priority with Pre-Submission Facility Correspondence	8 Months	5	239	239 to 239	100%

*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 participates in or leads product-specific meetings (1) to ensure efficient and effective communications between sponsors and FDA's review staff and between FDA's review staff from different Centers, (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 premarket review actions from FY 2020 to FY 2024 are presented in Table 24. In particular, in FY 2024, OCP received 270 requests for product-specific assistance, the responses to which contributed to ensuring the timely, effective, and aligned review of combination products.

Table 24. Number of OCP's Premarket Activities from FY 2020 to FY 2024.

	FY 20	FY 21	FY 22	FY 23	FY 24
Premarket Review Activities	188	124	160	222	270

Notably, in FY 2024, premarket product specific issues addressed by OCP included the following:

- Clarification of submission pathways and related development considerations for investigational combination products with separately distributed constituent parts;
- Regulatory considerations for the review of combination products for biosimilar prefilled autoinjectors;
- Cross-Center review consistency and process alignment when the submissions of two marketing applications for combination products are appropriate;
- Development considerations for the addition of a new indication or new combination product design for an approved combination product; and
- Clarification for the use of and type of master files for a constituent part.

In addition to addressing these issues, OCP completed the following premarket activities during FY 2024:

- OCP provided recommendations for how master file holders may engage with the Agency regarding master files related to generic combination products;

- OCP assisted the Centers and industry on regulatory and product-specific scientific issues relating to specific combination products or to specific categories of combination products;

- OCP provided considerations for when a clinical bridging study might be appropriate;

- OCP helped explain the type of submission needed for an investigational combination product with off-label use of a constituent part; and

- OCP hosted meetings with interested parties from industry to explore pharmacokinetic and platform device leveraging considerations.

Additional examples of these activities are presented in Table 25.

Table 25. Other Significant Premarket Review Facilitation or Assistance Provided by OCP in FY 2024.

Type of Activity	FY 2024 Accomplishments
Providing Significant Premarket Review Facilitation or Assistance	OCP provided significant assistance with: • Novel injector delivery systems (e.g., intranasal systemic delivery); • Explanation of expectations for current good manufacturing practice (CGMP) requirements under 21 CFR part 4; • The IND submission process for review and feedback for human factors validation protocols or Use Related Risk Analysis; • Aligning the IND and IDE review requirements for combination products; • The suitability of a single application for a combination product or a separate application for each constituent part; • The consistency of the review of on-body wearable injection or infusion systems; • The consistency in the review of combination products that include software; • The consistency of the review of bridging or leveraging proposals to add a new combination product design or new users for the same combination product; and • Facilitating resolution of informal timeliness or decision outcome disagreements between the review team members or with the application holder.

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.

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 detect, prevent, and respond quickly to product safety or quality problems, thereby minimizing the risk of these problems for patients and other users. Manufacturing controls and activities to assess CGMP compliance, such as facility inspections, help ensure that marketed products remain safe and effective. Postmarket surveillance activities, including postmarketing safety reporting, are also critical to protect patients from the risks associated with products currently on the market. Combination products pose particular challenges due to their complexity and to the range of scientific, technical, and regulatory issues that can arise.

OCP undertakes a variety of activities related to manufacturing controls and postmarket surveillance to help ensure the safety and quality of combination products. These activities include the following:

- Facilitating and leading the Agency's efforts to develop and publish regulations, guidance documents, compliance programs, and other public-facing documents regarding 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;

- Facilitating and leading meetings between industry and FDA regarding these matters; and

- Working with other Agency components to train staff, develop procedures, and update IT systems to enhance the efficiency and consistency of postmarket regulatory activities.

In addition, OCP may provide support for FDA's CGMP facility inspections and FDA's inspections 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 FY 2024, OCP's postmarket programmatic work included the following:

- Supporting Centers' development of regulations and guidance on device quality system and drug postmarket safety reporting;
- Engaging with the Centers and ORA[23] on data gathering and analysis relating to the tracking of combination products, the inspection of manufacturing facilities, and their assessment of postmarket safety events;
- Supporting the training of the Agency's postmarket staff; and
- Enhancing the Agency's IT systems to support the work of FDA's postmarket staff.

(See Section VI for a further discussion of OCP's postmarket policy activities in FY 2024.)

OCP's FY 2024 product-specific actions related to the consistency and appropriateness of its postmarket regulatory activities are reflected in Table 26.

Table 26. Product-Specific Postmarket Regulatory Activities from FY 2020 to FY 2024.

	FY 20	FY 21	FY 22	FY 23	FY 24
Postmarket Regulatory Activities	113	84	39	21	38

OCP engaged in 38 product-specific, postmarket-related 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. In addition, at the request of the Centers, OCP facilitated the Centers' assessments of safety signal evaluations to determine the Agency's response to the safety issue or by explaining product specific postmarket reporting requirements for specific constituent parts of a combination product.

[23] All references in this report to the Office of Regulatory Affairs (ORA) reflect the organization as it existed during FY 2024. ORA was reorganized into the Office of Inspections and Investigations (OII) effective October 1, 2024.

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

- Clarifying interested parties' and FDA's understanding of combination product CGMP requirements and inspectional approaches; and

- Facilitating the implementation of combination products' requirements under the PMSR final rule.[24]

[24] 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[25]. 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 2024. 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.

[25] See guidance Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product (May 2004) available at

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-and-resolution-formal-disputes-regarding-timeliness-premarket-review-combination-product

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 2024 are discussed below and included in the tables to follow.

A. Supporting and Implementing Legislative Initiatives

OCP continued to participate in the development of FDA's positions in response to congressional inquiries. OCP also continued its efforts, in coordination with the human medical product Centers, to implement section 3038 of the Cures Act regarding combination products. In addition, OCP continues to engage in the implementation of activities related to PDUFA VII for combination products (e.g., digital health, developing bridging guidance revisions, and clarifying the approach for human factors use related risk analysis).

OCP participated in the cross-FDA working group to develop 1) draft and final reports and implementation plans on identifying best practices for the efficient prioritization, development, issuance, and use of guidance documents and 2) a draft report and implementation plan on practices to broadly communicate externally as required by Section 2505 of the Consolidated Appropriations Act, 2023.

B. Streamlining Regulations

In addition, OCP supported rulemakings related to combination products that were led by the human medical product Centers, including rulemakings on (1) medical gases, (2) the amendment of device quality system regulations, and (3) any associated adjustments to CGMP requirements for combination products under 21 CFR part 4.

C. Clarifying Regulatory Policies

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

In FY 2024, OCP led the development and publication of the draft guidance *Essential Drug Delivery Outputs (EDDO) for Devices Intended to Deliver Drugs and Biological Products*.[26] Also, OCP led the revision and publication of the guidance *Application User*

[26] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/essential-drug-delivery-outputs-devices-intended-deliver-drugs-and-biological-products

Fees for Combination Products.[27] In addition, OCP contributed to the development and publication of the draft guidance *Purpose and Content of Use-Related Risk Analyses for Drugs, Biological Products, and Combination Products.*[28]

D. Other Policy-Related Activities

Additional policy-related activities included the following:

- Conducting performance evaluations and updates of procedural and IT systems to enable the implementation of the final PMSR rule for combination products; and
- Supporting implementation of the compliance program for combination product CGMPs.

Tables 27 through 29 identify FDA's policy development work that continued in FY 2024; this work is categorized by topic area (i.e., jurisdiction, premarket review, postmarket regulation) and activity type.

Table 27. Additional Jurisdictional Regulatory Initiatives.

Type of Activity	FY 2024 Activities
Developing regulations, guidance documents, and related information	OCP's jurisdiction-related activities included participating in the following Agency rulemaking and guidance document initiatives: • Continued to lead policy considerations for the scope and significance of cross-labeled combination products; • Led updates to the guidance document on the preparation of Pre-RFDs; and • Consideration for the jurisdiction assignment of medical maggots and medicinal leeches

[27] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/application-user-fees-combination-products

[28] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/purpose-and-content-use-related-risk-analyses-drugs-biological-products-and-combination-products

Type of Activity	FY 2024 Activities
Participating in other inter-Center and Agency-wide working groups to clarify issues related to product jurisdiction	OCP continued to enhance the efficiency and transparency of the RFD and Pre-RFD programs.

Table 28. Additional Premarket Review Regulatory Initiatives.

Type of Activity	FY 2024 Activities
Developing regulations, guidance documents, and policy documents	OCP's premarket review-related activities included leading the following Agency rulemaking and guidance document initiatives: • Continued to consider scope of revisions for the development of a final guidance document on the technical considerations for demonstrating the reliability of combination product emergency-use injectors; • Continued to lead the development and publication of the draft guidance document on essential drug delivery outputs for drug delivery devices; • Continued to lead the development of a draft guidance document on insulin pump labeling; • Continued to lead the development and publication of the update to a final guidance document on the application of user fees for combination products; and • Continued to lead the development of a draft guidance document on unique device identifier requirements for combination products.
Participating in other inter-Center and Agency-wide working groups or related activities to clarify issues related to combination products	OCP led or participated in working groups, or otherwise participated with Centers and other Agency components regarding the following: • Artificial intelligence (e.g., AI action plan; digital health/AI glossary) • Biosimilar/interchangeable biological products; • Application of artificial intelligence and machine learning for drug development; • Artificial intelligence-enabled device software functions: lifecycle management and marketing submission recommendations; • Issues such as importation of medical products and enforcement policies;

Type of Activity	FY 2024 Activities
	• Considerations for compounded drugs for use with devices; • Predetermined change control plans for devices; • Developing bridging guidance revisions; • National Drug Code (NDC) creation, assignment, listing and appropriate use for human drugs including biological products; • Responding to form 483 observations at the conclusion of a drug CGMP inspection; • Revising the National Drug Code format and drug label barcode requirements; • Advanced manufacturing technologies; and • Risk management plans to mitigate potential drug shortages.
Conducting procedural oversight and facilitation and other activities	• OCP continued to lead a working group regarding the monitoring and continuous improvement of the inter-Center consult process, including IT developments and enhancements; and • OCP continued to chair a cross-Center working group to develop procedures for standardizing and improving 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 2024 Activities
Leading or participating in other Inter-Center and Agency-wide working groups and other activities to clarify issues related to combination products	OCP's postmarket review-related activities included participating in the following Agency rulemaking, guidance document, and other initiatives: • OCP supported the development of a final rule to amend 21 CFR part 820 to align more closely with International Organization for Standardization 13485 and associated amendments to 21 CFR part 4; • OCP continued to chair a working group relating to the PMSR requirements for combination products. This group facilitates the consideration and resolution of postmarket combination product issues across OCP and the Centers. Additionally, OCP continued to support work on Center PMSR regulatory efforts, as well as develop and deliver internal training on PMSR; • OCP continued to co-chair a committee of the Association for the Advancement of Medical Instrumentation (AAMI). This committee's ongoing work on combination products related to best manufacturing practices, the training of regulated entities' staff on combination product regulations, and best practices across the combination products' lifecycle; and • OCP continued to participate in an American Society for Testing and Materials (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 Initiatives

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 interested parties.

- OCP implemented seven enhancement releases in FY 2024 to improve the inter-Center consult request workflow and data capture system, including changes to many consult types to offer additional options for both premarket and postmarket consults. In addition, updates to the inter-Center consult request form improved the user experience by providing more complete and accurate consult information. Also, two-way integration was developed between the inter-Center consult request system and CDER's regulatory review systems, which has increased efficiency and improved data quality due to sharing of information.

- OCP implemented five enhancement releases in FY 2024 to improve the combination product PMSR dashboard's functionality and user experience. This dashboard, 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; this integration enhances the efficiency and consistency of postmarket safety activities. Examples of enhancements in these releases included user interface changes to improve the user experience, updating the connection to an existing data source, and developing extensive training resources available throughout the dashboard.

- OCP implemented two enhancement releases for FY 2024 to improve the electronic system that manages the workflow and data capture for Pre-RFD and RFD reviews and decisions. Examples of enhancements included (1) adding a new permission set for specified users, (2) improving the efficiency of the system-generated notifications by updating the language, (3) updating the Pre-RFD numbering process to ensure consistency across the system, and (4) adding prescribed descriptive language to all attachments received per submission.

- OCP provided trainings, demonstrations, user guides, and other resources to new and current users from OCP and all three human medical product Centers for all OCP-led systems. OCP also engaged users through surveys, 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., the Combination Products Coalition, the Advanced Medical Technology Association) that represent the drug, device, biological product, and combination product industries. OCP's discussions with these trade associations and coalitions involved FDA's classification, assignment, and regulation of combination products, as well as other related regulatory topics. These discussions have enhanced communication between the Agency and external interested parties and help FDA address questions or challenges faced by sponsors developing combination products.

In addition, OCP participates in national and international standards development organizations in conjunction with FDA Centers, including co-chairing a committee on combination products for the AAMI and supporting the work of the International Organization for Standardization, ICH, International Medical Device Regulators Forum, and ASTM International. OCP also engages with foreign counterparts in conjunction with FDA Centers and Office of Global Policy and Strategy regarding opportunities for convergence and on outreach regarding shared goals for holistic risk management across the lifecycle of different types of medical products intended for combined use with one another.

OCP presents at various industry conferences. These conferences offer opportunities for Agency officials to engage with interested parties, to clarify areas of interested party confusion, and to learn about interested party questions and concerns that may warrant investigation and, if needed, the development of policy by FDA to address those concerns.

In FY 2024, FDA addressed a wide range of topics about which interested parties had questions, concerns, or proposals for Agency consideration. These topics included emerging issues in combination product regulation and the broader area of the combined use of separately distributed medical products; opportunities for regulatory convergence across jurisdictions; 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 interested party priorities for further action.

Examples of OCP's FY 2024 outreach activities via industry conferences are included in Table 30.

Table 30. Examples of FY 2024 Outreach Activities.

Type of Activity	FY 2024 Accomplishments
Presentations and outreach activities	The following are examples of venues/events for which OCP provided presentations and/or educational outreach: • Orange County Regulatory Affairs Discussion Group (Aug. 2024); • Medtech & Pharma Platform (MPP) 2024 Annual Conference (September 2024); • RAPS/AFDO Combination Products Summit (November 2023); • Food and Drug Law Institute (FDLI) (May 2024); • The Organisation for Professionals in Regulatory Affairs (TOPRA) (October 2023); • TOPRA - Continuing Regulatory Education and Development (CRED) Workshop (March 2024); • Medical Device Manufacturers Association (MDMA) 2024 FDA Forum (March 2024); and • Served as conference co-chair for the RAPS/AFDO Combination Products Summit.

Appendix A: FY 2023 Updated Performance Detail

The table below reflects the final list of 598 original applications classified into one of nine categories of combination products received in FY 2023, after corrections and actions as of September 30, 2024. Note, this updated table includes the removal of single patient emergency use/compassionate use/expanded access study products that were initially counted in the FY 2023 report (see FN19).

Table 1. Workload by Combination Product Category Number.

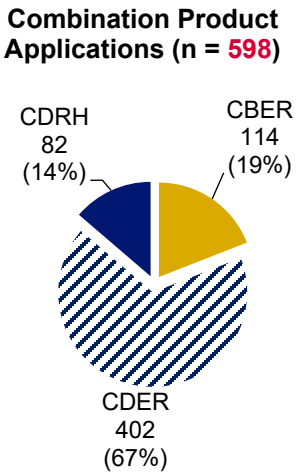
Application Type	1	2	3	4	5	6	7	8	9	Total
Original NDA	14	21	0	0	0	0	1	0	2	38
Original BLA	5	2	4	0	0	0	0	0	0	11
Original PMA	0	0	1	2	0	0	1	0	0	4
Original 510(k)	1	0	1	36	0	0	0	0	0	38
Original IND	55	44	79	4	7	51	8	41	16	305
Original IDE	0	4	1	31	11	1	0	0	5	53
Original HDE	0	0	0	0	0	0	0	0	0	0
Original ANDA	26	107	0	0	0	0	0	0	1	134
Biosimilar BLA	3	2	7	0	0	0	0	0	1	13
De Novo	1	0	0	1	0	0	0	0	0	2
Total	105	180	93	74	18	52	10	41	25	598

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 2023 by Center lead, as of September 30, 2024.



This report was prepared by FDA's Office of Combination Products in collaboration with FDA's Performance Management Staff; 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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This report is available on FDA's website at https://www.fda.gov/ and on OCP's home page at https://www.fda.gov/combination-products.