Performance Report to Congress

Office of Combination Products

FY 2023

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

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) 2023 (i.e., October 1, 2022, to September 30, 2023). This report highlights the following OCP activities for FY 2023:

A. Prompt Assignment of Combination Products

Sponsors may submit a Request for Designation (RFD) 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 2023, OCP issued four combination product and four 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 2023, OCP provided classification and Center assignment feedback for 60 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 2023, OCP conducted several activities related to the premarket review of combination products. For instance, OCP received 222 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 2023, FDA received 735 original premarket applications for combination products. There were 1,199 inter-Center consulting reviews for combination products in FY 2023. (For more information, see the "Policy and Procedural Activities and Accomplishments" section below.)

C. Consistent and Appropriate Postmarket Regulation

In FY 2023, OCP provided clarification and support for 21 separate postmarket matters. OCP continued to chair FDA working groups to address current good manufacturing practices and postmarketing safety reporting 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 2023, 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 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.

For example, OCP published the final guidance document *Application of Human Factors Engineering Principles for Combination Products: Questions and Answers (September 2023)*.[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 postmarketing safety reporting dashboard.

OCP also continued, in FY 2023, to conduct external outreach activities through engagement with external organizations and through a variety of educational and

[2] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/application-human-factors-engineering-principles-combination-products-questions-and-answers.

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 interested organizations can engage with FDA on these issues; enable FDA to understand and respond to questions and concerns from interested organizations; 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
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	U.S. Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
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
OCE	Oncology Center of Excellence
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 the U.S. Food and Drug Administration (FDA or Agency) to establish an office "to ensure the prompt assignment of combination products to Agency Centers, the timely and effective premarket review of such products, and consistent and appropriate postmarket regulation of like products 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 (FD&C 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 FD&C 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 2023 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 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 fiscal year (FY) 2023 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
    - 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

[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.

- 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, 2023.

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 2019 to FY 2023

OCP received 66 RFD submissions in FY 2023. Of the 66 total RFD submissions that were received and reviewed in FY 2023, seven RFD submissions (11%)[8] had a decision issued, 54[9] RFD submissions (82%) were found to have insufficient information for

[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.

[9] Two of the 66 RFD submissions were received at the end of FY 2023 with a filing decision due date in FY 2024. In FY 2024, these two RFDs were found to have insufficient information for filing.

filing, three RFD submissions (4%) were withdrawn[10] by the sponsor, and two RFD submissions (3%) were still being reviewed within the 60-day review period at the close of FY 2023.[9] One RFD submission received in FY 2022 was completed in FY 2023. Of the eight RFD determinations made in FY 2023, four were classified as combination products, and four 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 2023 is compared to the previous 5 years.

Table 1. RFD Determinations from FY 2019 to FY 2023.

RFD Submissions	FY 19	FY 20	FY 21	FY 22	FY 23
Total RFD Combination Product Classifications/ Assignments	7	7	1	2	4
Total RFD Non-Combination Product Classifications/ Assignments	6	2	2	2	4

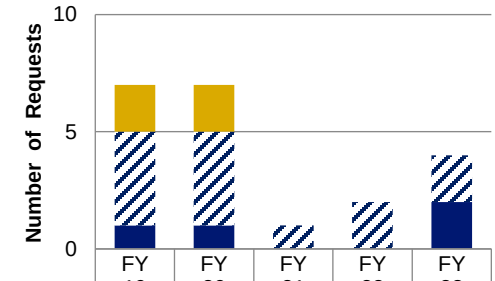
In FY 2023, the eight RFD determinations were all issued by the statutorily mandated 60-day deadline. The average RFD review time was 59 days, with a median review time of 60 days. Two RFD determinations classified the products as device-drug combination products. One RFD determination classified the product as a device-drug-biologic combination product. One RFD determination classified the product as a drug-biologic combination product. Four RFD determinations classified the products as non-combination products: three were drugs and the other was a biological product.

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

As shown in Table 2, the total number of RFD combination product Center assignment determinations in FY 2023 increased by two from FY 2022.

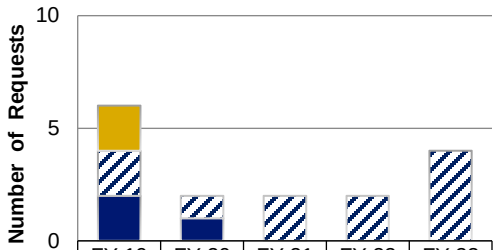
As shown in Table 3, the total number of RFD non-combination product Center assignment determinations in FY 2023 increased by two from FY 2022.

Table 2. Combination Product Assignment Determinations.



	FY 19	FY 20	FY 21	FY 22	FY 23
Total	7	7	1	2	4
CBER	2	2	0	0	0
CDER	4	4	1	2	2
CDRH	1	1	0	0	2

Table 3. Non-Combination Product Assignment Determinations.



	FY 19	FY 20	FY 21	FY 22	FY 23
Total	6	2	2	2	4
CBER	2	0	0	0	0
CDER	2	1	2	2	4
CDRH	2	1	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	2	100%
Drug-Biologic	1	NA
Device-Biologic	0	NA
Device-Drug-Biologic	1	NA
Total	**4**	**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 2023.

Table 5. Timeliness of Non-Combination Product Determinations.

Determination	Product Assignments Issued*	Percent On Time*
Drug	3	100%
Biologic	1	100%
Device	0	NA
Total	**4**	**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 2023.

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 2019 to FY 2023.

Table 6. OCP's Pre-RFD Workloads from FY 2019 to FY 2023.

Pre-RFD Assessment Decisions	FY 19	FY 20	FY 21	FY 22	FY 23
Combination Product Assessments	51	47	30	30	31
Non-Combination Product Assessments	29	30	15	19	28
Unclassified Assessments*	3	2	1	0	1[11]
Total Pre-RFD Assessments	83	79	46	49	60

* 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 the sufficient information needed for FDA to initiate an assessment. OCP received 94 Pre-RFD submissions in FY 2023. Of the 94 received, 29 Pre-RFD submissions (31%) were completed, 33 Pre-RFD submissions (35%) were reviewed and not accepted due to their lack of sufficient information for OCP to complete an assessment, and nine Pre-RFD submissions (9%) were withdrawn[12] by the sponsor.[10] The remaining 23 Pre-RFD submissions (24%) received in FY 2023 are under FDA's review, and their review timeline overlaps into FY 2024.[13] Some of these 23 Pre-RFD submissions were impacted by FDA's pending 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

[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] Prior to receiving withdrawal requests from the sponsors, five Pre-RFDs had not been screened, and four were "not filed" after screening.

[13] The 23 Pre-RFD submissions overlapping into FY 2024 will be reported on in the FY 2024 OCP performance report.

Act.[14] In FY 2023, OCP completed the review of 60 total Pre-RFDs, of which 29 were received in FY 2023, 25 were received in FY 2022[15] and six were received in FY 2021.[16] Twenty-six Pre-RFD assessments (43%) 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 125 days, with a median review time of 70 days.[14]

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; 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), this 60-day goal may not be possible. FDA's achievement of goal timeframes is commensurate with available resources. Additionally, as previously mentioned, several Pre-RFD submissions were impacted by FDA's pending 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. The uncertainty from these considerations delayed their evaluation.

[14] On April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit issued the *Genus Medical Technologies*, *LLC* decision, holding that FDA cannot classify as a *drug* any product that meets the *device* definition in section 201(h) of the FD&C Act. A *Federal Register* notice about this decision, issued in August 2021, is 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. In addition, section 3621 of the Food and Drug Omnibus Reform Act of 2022 (enacted on December 29, 2022), amended section 503 of the FD&C Act by adding subsection (h), which specified that certain products were deemed to be drugs under section 201(g) and not devices under section 201(h) of the FD&C Act.

[15] The initial submissions of the 25 Pre-RFDs received in FY 2022 lacked sufficient information to be accepted by FDA for review. After several iterations of Additional Information requests to the sponsors, 15 were accepted for review in FY 2023, and the other 10 had their reviews completed in FY 2023. Some of these Pre-RFD submissions were also impacted by FDA's pending 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.

[16] The initial submissions of the six Pre-RFDs received in FY 2021 lacked sufficient information to be accepted by FDA for review. After several iterations of Additional Information requests to the sponsors, two were accepted for review in FY 2023, and the other four had their reviews completed in FY 2023. Some of these Pre-RFD submissions were also impacted by FDA's pending 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.

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	25	48%
Drug-Biologic	0	N/A
Device-Biologic	2	0%
Drug-Device-Biologic	4	50%
Total	31	48%

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	23	57%
CBER	2	0%
CDRH	6	33%
Total	31	48%

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	9	12%
Biologic	6	33%
Device	10	70%
Other	3[17,18]	0%
Total	28	36%

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	13	15%
CBER	5	40%
CDRH	8	75%
Other	2[19]	0%
Total	28	36%

[17] *HCT/Ps* stands for human cells, tissues, and cellular and tissue-based products. HCT/Psconsist of human cells or tissues intended for implantation, transplantation, infusion, or transfer into a human recipient. HCT/Ps that meet all of the criteria in 21 CFR 1271.10(a) are subject only to regulation under section 361 of the Public Health Service Act and the regulations in 21 CFR part 1271. An HCT/P that falls into this category is sometimes referred to as a *361 HCT/P*, and no premarket authorization is required.

[18] Three Pre-RFDs were not given a classification. The first Pre-RFD failed to meet the criteria for 361 HCT/P, which was the specific determination requested by the sponsor. The second Pre-RFD was incorrectly entered as a Pre-RFD but was determined to be a cosmetic. The third Pre-RFD included two distinct products, which, when combined at point of sale, created a new drug.

[19] For these two Pre-RFDs, the first was not assigned to a Center because the specific request from the sponsor was to determine if the product met the criteria for 361 HCT/P. The second Pre-RFD was determined to be a cosmetic.

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 2023.

Center Assignment	FY 20	FY 21	FY 22	FY 23
CDER	44	35	35	37
CBER	4	8	7	4
CDRH	27	23	12	7
Unassigned*	4	33[20]	21	27
Total	79	99	75	75

* 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.

[20] 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.

Table 12. Number of OCP's Additional Product Classification and Center-Assignment Activities from FY 2020 to FY 2023.

	FY 20[21]	FY 21	FY 22	FY 23[22]
Jurisdiction/Classification Activities	950	375	235	147

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

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

C. OCP's FY 2023 Activities and Accomplishments

Table 13 highlights OCP's Activities for classification and Center-assignment for FY 2023.

Table 13. Specific FY 2023 Activities by OCP.

Type of Activity	FY 2023 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, 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 standards for cross-labeled combination product classification and Center assignment, (2) clarifying the regulatory status of software used with a drug or biological product, (3) determining when container/closures are also considered devices, (4) classifying articles that meet both the *biological product* and *device* definitions, and (5) classifying the elements of the systems used at the point of care.
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 21 CFR part 3 for clarity and consistency with more recent judicial, 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").[23] 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 2023, 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 2023 by CBER, CDER, and CDRH (including submissions filed or received in FY 2023), as well as the timeliness of these reviews.

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

[23] 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 2019 to FY 2023

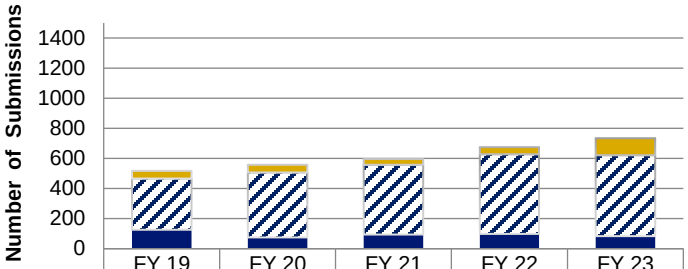
As shown in Table 14, 735 original applications were submitted for review in FY 2023.

Table 14. FY 2019 to FY 2023 Submission Review Workloads.

Submission/Request	FY 19	FY 20	FY 21	FY 22	FY 23
Total Combination Products Submitted for Review	518	557	596	674[24]	735

As reflected in Table 15, of the original combination product applications received, 73% were received by CDER, 11% were received by CDRH, and 16% were received by CBER. The increase in combination product applications received by CBER between FY 2021 and FY 2022 can be attributed to its updated tracking procedures.

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



	FY 19	FY 20	FY 21	FY 22	FY 23
Total	518	557	596	674	735
CBER	53	50	39	47	114
CDER	339	432	464	528	537
CDRH	126	75	93	99	84

Table 16 presents the 735 original applications for combination products received in FY 2023, broken down by the identified 10 application types and by the product's initial classification into one of nine categories of combination products.[24] The same table reflecting applications received in FY 2022 has been updated in Appendix A to reflect corrections and actions as of September 30, 2023. The majority of the applications received in FY 2023 were original investigational new drug applications (INDs) (60%), followed by ANDAs (19%). Also, the most common combination product category was the pre-filled drug delivery device/system (25%).

[24] 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). See Appendix A for updated numbers for FY 2022.

Table 16. Workload by Combination Product Category Number.

Application Type	1	2	3	4	5	6	7	8	9	Total
Original NDA	14	17	1	0	0	0	1	0	2	35
Original BLA	5	2	1	0	0	0	0	0	4	19
Original PMA	1	0	0	2	0	0	0	0	1	4
Original 510(k)	1	0	0	36	0	0	0	0	1	38
Original IND	59	55	103	4	7	144	10	45	16	443
Original Investigational Device Exemption (IDE)	0	4	1	31	11	1	0	0	7	55
Original Humanitarian Device Exemption (HDE)	0	0	0	0	0	0	0	0	0	0
ANDA	30	109	0	0	0	0	0	0	0	139
Biosimilar BLA	2	0	5	0	0	0	0	0	0	8
De Novo	1	0	0	1	0	0	0	0	0	2
Total	113	187	111	74	18	145	11	45	31	735

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.[25]

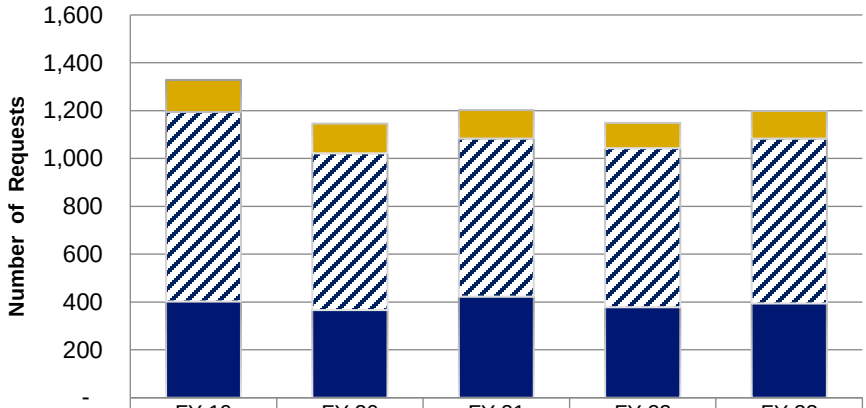
OCP oversees and facilitates coordination among review Centers under the inter-Center consult process to ensure consults are completed in a timely manner. For example, OCP monitors ongoing inter-Center consult requests for correctness (e.g., ensuring the information in the consult requests are complete 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 2023, there were 1,199 inter-Center consults for combination products. Table 17 shows the number of FY 2023 inter-Center consults requested by each Center.

[25] 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 (OCE)). 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 19	FY 20	FY 21	FY 22	FY 23
Total	1,328	1,146	1,202	1,149	1199
CBER	133	124	119	106	115
CDER	792	656	661	665	689
CDRH	403	366	422	378	395

In Table 18, the total number of inter-Center consults in FY 2023 compared to the previous 5 years.

Table 18. FY 2019 to FY 2023 Inter-Center Consult Workloads.

Submission/Request	FY 19	FY 20	FY 21	FY 22	FY 23
Total Inter-Center Consult Requests	1,328	1,146	1,202	1,149	1,199

In Table 19, the number of inter-Center consult requests during FY 2023 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	--	36	77	1	1	--	115
CDER	9	--	680	--	--	--	689
CDRH	6	387	--	--	--	2	395
Total	15	423	757	1	1	2	1,199

* 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 Inter-Center Consults by Application Type and Lead Center.*

Application Type	Lead Center			
	CBER	CDER	CDRH	Number of Consults
ANDA	--	100	--	100
BLA	25	125	--	150
IND/Pre-IND	78	345	--	423
NDA	--	119	--	119
510(k)	1	--	19	20
De Novo	--	--	5	5
IDE	1	--	106	107
PMA	--	--	98	98
Pre-Submission	--	--	163	163
Other**	10	--	4	14
Total	115	689	395	1,199

* 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).

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 2022 and FY 2023 Review Performance Results," updates FDA's final review performance results on the FY 2022 combination product submissions and presents FDA's preliminary[26] review performance results on the FY 2023 combination product submissions through September 30, 2023.

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

D. FY 2022 and FY 2023 Review Performance Results

Table 22 shows the final[27] FY 2022 review goal performance results. Review goal performance data are based on the fiscal year receipt cohort.

Table 22. Final FY 2022 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	211	133 to 851	86%
NDAs	Standard	10 Months	20	304	42 to 412	100%
BLAs	Priority	6 Months	6	243	231 to 333	100%
BLAs	Standard	10 Months	5	365	294 to 671	100%
Biosimilar BLAs	Standard	10 Months	6	365	365 to 748	83%
Expedited and Original PMAs	Standard	180 or 320 Days†	3	179	178 to 248	50%
510(k)s	Standard	90 Days	46	83	0 to 331	72%
De Novos	Standard	150 Days	0	N/A	N/A	N/A
ANDAs	Standard	10 Months	114	302	284 to 569	91%
ANDAs	Priority without Pre-Submission Facility Correspondence	10 Months	36	301	238 to 650	88%
ANDAs	Priority with Pre-Submission Facility Correspondence	8 Months	9	238	226 to 244	100%

* This NDA was closed after 6 days because the user fees were not paid.
** 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.

[27] *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 2023 review goal performance results through September 30, 2023.

Table 23. Preliminary 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	83%
NDAs	Standard	10 Months	24	348.5	57 to 392	100%
BLAs	Priority	6 Months	6	243	182 to 322	100%
BLAs	Standard	10 Months	4	293	60 to 364	100%
Biosimilar BLAs	Standard	10 Months	9	364	352 to 456	100%
Expedited and Original PMAs	Standard	180 or 320 Days†	3	177	172 to 213	67%
510(k)s	Standard	90 Days	37	60	23 to 90	100%
De Novos	Standard	150 Days	2	82	14 to 150	100%
ANDAs	Standard	10 Months	108	303	238 to 464	100%
ANDAs	Priority without Pre-Submission Facility Correspondence	10 Months	26	366	267 to 482	100%
ANDAs	Priority with Pre-Submission Facility Correspondence	8 Months	5	251	228 to 386	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 leads or participates in 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 2019 to FY 2023 are presented in Table 24. In particular, in FY 2023, OCP received 222 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 2019 to FY 2023.

	FY 19	FY 20	FY 21	FY 22	FY 23
Premarket Review Activities	144	188	124	160	222

Notably, in FY 2023, 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;
- Alignment of data considerations for simulated shipping studies and sharps protection features;
- 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; 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 2023:

- OCP continued to lead an inter-Center working group to align the Agency master file processes;

- OCP provided clarifications for the appropriate type of premarket meeting with a master file holder on the proper use of master files for 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, and.

- OCP hosted meetings with industry groups to explore pharmacokinetic and platform device leveraging considerations.

Examples of these activities are presented in Table 25.

Table 25. Other Significant Premarket Review Facilitation or Assistance Provided by OCP in FY 2023.

Type of Activity	FY 2023 Accomplishments
Providing Significant Premarket Review Facilitation or Assistance	OCP provided significant assistance with: • Novel drug-device cancer therapies or treatment delivery technologies; • Injector delivery systems (e.g., intranasal systemic delivery); • Current good manufacturing practice (CGMP) requirements under 21 CFR part 4; • The IND human factors validation protocol or the Use Related Risk Analysis submission process for IND submissions; • 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 and combination products that includes software; • Facilitating the resolution of timeliness or decision outcome disagreements between the review team and the application holder; • The compatibility of needleless syringes with a Luer-activated valve; and • Continued to provide clarifications for the CGMP regulatory requirements that apply to certain ophthalmic products in light of the ruling in *Genus Medical Technologies, LLC v. FDA* and subsequent legislation.

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 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;

- 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 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 FY 2023, OCP's postmarket programmatic work included the following:

- Leading or supporting Centers' development of regulations and guidance on CGMPs;
- Engaging with the Centers and ORA 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 2022.)

OCP's FY 2023 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 2019 to FY 2023.

	FY 19	FY 20	FY 21	FY 22	FY 23
Postmarket Regulatory Activities	62	113	84	39	21

OCP engaged in 21 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.

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

- Clarifying sponsors' 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.[28]

[28] 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.[29] 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 2023. 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.

[29] See the final guidance document *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 2023 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 and in the development of legislative proposals. 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 continued to engage in the implementation of activities related to PDUFA VII for combination products (e.g., digital health and developing bridging human factors use-related risk analysis).

B. Streamlining Regulations

OCP continued its active efforts to update and clarify FDA's jurisdictional regulations in 21 CFR part 3 in light of recent judicial, legislative, and policy developments. 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, notices, safety communications, and internal procedures.

In FY 2023, OCP led the development and publication of the final guidance document *Application of Human Factors Engineering for Combination Products: Questions and Answers* (September 2023).[30] In addition, OCP contributed to the development and publication of the final guidance document *Regulatory Considerations for Prescription Drug Use-Related Software* (September 2023).[31]

[30] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/application-human-factors-engineering-principles-combination-products-questions-and-answers.

[31] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-prescription-drug-use-related-software.

D. Other Policy-Related Activities

Additional policy-related activities included the following:

- Enhancing procedures and mechanisms for monitoring and enhancing combination products' premarket and postmarket regulatory activities, consistent with section 3038 of the Cures Act;

- 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 2023; 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 2023 Activities
Developing regulations and guidance documents	OCP's jurisdiction-related activities included participating in the following Agency rulemaking and guidance document initiatives: • Led policy development on the scope and significance of the status of cross-labeled combination products; and • Led updates to the guidance document on the preparation of Pre-RFDs.
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 2023 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 lead and completed the development of a final guidance document on human factors studies for combination products; • Continued to lead considerations 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 of a draft guidance document on essential performance requirements; • Continued to lead the development of a draft guidance document on insulin pump labeling; • Continued to lead the development of an 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. OCP participated in the development of the following policy documents: • Citizen petition responses for specific types of generic combination products; • Cross-Center draft guidance document on considerations for what constitutes clinical data for user fee purposes; and • Cross-Center draft guidance document on technical considerations for container closures that are also device constituent parts.

Type of Activity	FY 2023 Activities
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: • Biosimilar/interchangeable biological products; • Comparative analysis of generic combination products; • Application of artificial intelligence and machine learning for drug development; • Issues such as importation of prescription drugs, good guidance practices, and enforcement policies; and • Considerations for compounded drugs for use with devices.
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; • 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; and • OCP led ongoing efforts to revise inter-Center agreements on medical product Center assignment/regulatory coordination.

Table 29. Additional Postmarket Review Regulatory Initiatives.

Type of Activity	FY 2023 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 working groups relating to the PMSR requirements for combination products. These groups' work focused on implementing the rule, monitoring the engagement between the Centers and OCP on postmarket combination product issues, and developing and delivering internal training; • OCP continued to work with the Centers on track-and-trace programs with respect to combination products, including guidance document on the use of unique device identifiers, numeric drug codes, and serialized numeric identifiers; • OCP continued to co-chair a committee of the Association for the Advancement of Medical Instrumentation. 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, and in an ASTM process to address CGMP best practices for

Type of Activity	FY 2023 Activities
	combination products for the global market.

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 external groups.

- OCP implemented four enhancement releases in FY 2023 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.

- OCP implemented five enhancement releases in FY 2023 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 adding new fields, automating the connection to an existing data source, and developing extensive training resources available throughout the dashboard.

- OCP implemented three enhancement releases for FY 2023 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 and 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 organizations and help FDA address questions or challenges faced by sponsors developing combination products.

In addition, in conjunction with FDA's Centers, OCP participates 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 engages with foreign counterparts, in conjunction with FDA's 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 organizations, to clarify areas of confusion, and to learn about questions and concerns that may warrant consideration and, if needed, the development of policy by FDA to address those concerns.

In FY 2023, FDA addressed a wide range of topics about which interested organizations 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 priorities for further action.

Examples of OCP's FY 2023 outreach activities via industry conferences are included in Table 30.

Table 30. Examples of FY 2023 Outreach Activities.

Type of Activity	FY 2023 Accomplishments
Presentations and outreach activities	The following are examples of venues/events for which OCP provided presentations and/or educational outreach: • Association for the Advancement of Medical Instrumentation/FDA/British Standards Institute International Conference on Medical Device Standards (Oct. 2022); • Regulatory Affairs Professionals Society /Association of Food and Drug Officials Combination Products Summit (November 2022); • Drug Information Association Annual Conference (June 2023); and • Medtech & Pharma Platform 2023 Annual Conference (September 2023).

Appendix A: FY 2022 Updated Performance Detail

The table below reflects the final list of 674 original applications, classified into one of nine categories of combination products received in FY 2022, after accounting for corrections and actions as of September 30, 2023.

Table 1. Workload by Combination Product Category Number.

Application Type	1	2	3	4	5	6	7	8	9	Total
Original NDA	4	21	0	0	0	0	1	0	1	27
Original BLA	0	1	6	0	0	2	0	0	3	12
Original PMA	0	0	0	2	0	0	0	0	2	4
Original 510(k)	3	1	0	40	0	0	7	1	3	55
Original IND	129	34	61	6	1	43	10	55	20	359
Original IDE	4	1	0	34	5	1	3	1	4	53
Original HDE	0	0	0	0	0	0	0	0	0	0
Original ANDA	30	118	0	0	0	0	0	0	11	159
Biosimilar BLA	1	0	4	0	0	0	0	0	0	5
De Novo	0	0	0	0	0	0	0	0	0	0
Total	171	176	71	82	6	46	21	57	44	674

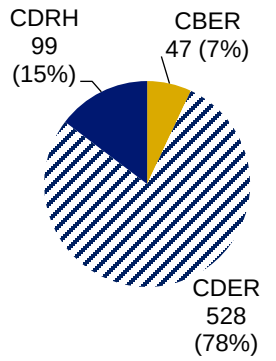
Combination Product Category Key:

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 2022 by Center lead, as of September 30, 2023.

Combination Product Applications (n = 674)



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

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