Performance Report to Congress

Office of Combination Products

FY 2022

(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) 2022 (i.e., October 1, 2021, to September 30, 2022). This report highlights the following OCP activities for FY 2022:

A. Prompt Assignment of Combination Products

Sponsors may submit Request for Designation (RFD) submissions to obtain formal Agency determinations for the classification of a human medical product (e.g., biological product, device, drug, or combination product) and/or for the Center assignment (i.e., the lead Center in the case of a combination product) for the product's premarket review and regulation. In FY 2022, OCP issued two combination product and two 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 2022, OCP provided classification and Center assignment feedback for 48 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 2022, OCP conducted several activities related to the premarket review of combination products. For instance, OCP received 160 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 2022, FDA received 600 original premarket applications for combination products. There were 1,149 inter-Center consulting reviews for combination products in FY 2022. (For more information, see the "Policy and Procedural Activities and Accomplishments" section below.)

C. Consistent and Appropriate Postmarket Regulation

In FY 2022, OCP provided clarification and support for 39 separate postmarket matters. OCP continued to chair FDA working groups to address current good manufacturing practices (CGMP) 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 2022, 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 staff 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 guidance documents related to principles of premarket pathways for combination products[2] and published, in the *Federal Register*, alternative or streamlined mechanisms to address CGMP requirements for these products.[3] Also, OCP issued system updates and provided 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 (PMSR) dashboard.

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[2] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-premarket-pathways-combination-products.

[3] 87 FR 56066 (Sep. 13, 2022), available at https://www.govinfo.gov/content/pkg/FR-2022-09-13/pdf/2022-19713.pdf.

OCP also continued, in FY 2022, to conduct external outreach activities through engagement with stakeholder organizations and through a variety of educational and informational presentations to national and international audiences and standard-setting bodies. These activities were intended to foster a greater understanding of the complex regulatory and scientific issues in the developmental, premarket, and postmarket settings for combination products; clarify how stakeholders can engage with FDA on these issues; enable FDA to understand and respond to stakeholders' questions and concerns; and identify potential areas for regulatory convergence across jurisdictions for FDA's oversight of combination products.

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Acronym List

510(k)	Premarket Notification
ANDA	Abbreviated New Drug Application
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.[4]

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

[4] 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[5] (i.e., devices, drugs, and biological products) and (2) incorporate cutting-edge, novel technologies that hold great promise for advancing patient care. Combination products may incorporate, for example, advanced delivery systems and may include personalized medicine drug-device combinations, biologic-device combinations, applications of nanotechnology, and other innovative technologies and scientific advancements.

B. Statutorily Mandated Functions of OCP

MDUFMA and the Cures Act have established broad responsibilities for OCP that cover the regulatory lifecycle from decisions relating to product jurisdiction to oversight and facilitative duties relating to the premarket review and postmarket oversight of combination products.[6] However, the primary day-to-day responsibilities for the premarket review and the postmarket regulation of combination products remain in the three human medical product Centers – the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH).

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

(1) Promptly assign a Center with primary jurisdiction for a combination product;

(2) Ensure the timely and effective premarket review of combination products by overseeing the timeliness of reviews and the alignment of the Agency's feedback to the sponsor and by coordinating reviews involving more than one Center;

[5] 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.

[6] Under the Prescription Drug User Fee Act Reauthorization of 2017 (PDUFA VI) commitments, FDA initiated an independent third-party assessment of FDA's regulatory activities for combination products, including premarket reviews. A final report from this assessment, issued in August 2020, is available at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vi-assessment-combination-product-review-practices-pdufa-vi. The report found FDA's jurisdictional, inter-Center consult request and premarket review practices for combination products fundamentally sound but offered recommendations to improve FDA's efficiency, to enhance FDA's practices through "straightforward" and "minor" refinements to processes, and to address technological challenges. These recommendations aligned with the Agency's ongoing efforts to improve and enhance these practice areas. OCP continues to implement the recommendations as discussed in this FY 2021 Performance Report.

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

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

(5) Review and modify/revise/eliminate, as needed, agreements, guidance documents, or practices specific to the assignment of combination products.

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

In addition, OCP has responsibility for FDA's actions on all Requests for Designation (RFDs) submitted by industry in accordance with 21 U.S.C. 360bbb-2 and 21 CFR part 3, "Product Jurisdiction." 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 2022 activities and accomplishments, including its fulfillment of statutory mandates. This report presents information and data on OCP's activities related to the following:[7]

- Prompt assignment of combination products
    - Timeliness of the classification and assignment of combination products
- Timely and effective premarket review
    - Number and types of combination products under review
    - Timeliness of the reviews of combination products
    - Number of premarket reviews of combination products that involved a

[7] 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.

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, 2022.

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.[8] 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 2017 to FY 2022

OCP received 41 RFD submissions in FY 2022. Of the 41 total RFD submissions that were received and reviewed in FY 2022, four RFD submissions (10%)[9] had a decision issued, 35[10] RFD submissions (85%) were found to have insufficient information for filing, one RFD submission (2%) was withdrawn by the sponsor, and one RFD submission (2%) was within the 60-day review period at the close of FY 2022. Of the

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

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

[10] Two of 35 RFD submissions were received at the end of FY 2022 with a filing decision due date in FY 2023. In FY 2023, these two RFDs were found to have insufficient information for filing.

four RFD determinations, two were classified as combination products and two 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 2022 is compared to the previous 5 years.

Table 1. RFD Determinations from FY 2017 to FY 2022.

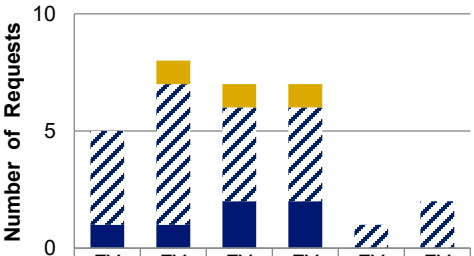
RFD Submissions	FY 17	FY 18	FY 19	FY 20	FY 21	FY 22
Total RFD Combination Product Classifications/ Assignments	5	8	7	7	1	2
Total RFD Non-Combination Product Classifications/ Assignments	3	0	6	2	2	2

In FY 2022, the four RFD determinations were all issued by the statutorily mandated 60-day deadline. The average RFD review time was 58 days, with a median review time of 58 days. Two RFD determinations classified the products as drug-device combination products. Two RFD determinations classified the products as non-combination products, one as a drug and the other one as a biological product.

As shown in Table 2, the total number of RFD combination product Center assignment determinations in FY 2022 increased by one from FY 2021.

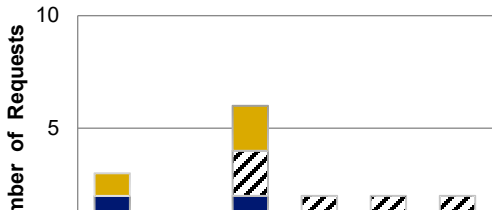
As shown in Table 3, the total number of RFD non-combination product Center assignment determinations in FY 2022 remained the same as in FY 2021.

Table 2. Combination Product Assignment Determinations.



	FY 17	FY 18	FY 19	FY 20	FY 21	FY 22
Total	5	8	7	7	1	2
CBER	0	1	1	1	0	0
CDER	4	6	4	4	1	2
CDRH	1	1	2	2	0	0

Table 3. Non-Combination Product Assignment Determinations.



	FY 17	FY 18	FY 19	FY 20	FY 21	FY 22
Total	3	0	6	2	2	2
CBER	1	0	2	0	0	0
CDER	0	0	2	1	2	2
CDRH	2	0	2	1	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*
Drug-Device	2	100%
Drug-Biologic	0	NA
Device-Biologic	0	NA
Drug-Device-Biologic	0	NA
Total	**2**	**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 2022.

Table 5. Timeliness of Non-Combination Product Determinations.

Determination	Product Assignments Issued*	Percent On Time*
Drug	1	100%
Biologic	1	100%
Device	0	NA
Total	**2**	**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 2022.

1. Pre-RFD Workload Performance Results

OCP continues the Pre-RFD program[11] to provide preliminary feedback for product classifications and Center assignments (i.e., Pre-RFD assessments). The Pre-RFD process offers more flexibility than the RFD process, allowing for more discussions between FDA and a sponsor if questions arise during the review. Table 6 shows OCP's Pre-RFD submission review workloads from FY 2017 to FY 2022.

[11] Formalization of the Pre-RFD program as a distinct OCP activity occurred during FY 2016. Consistent with past practice, Pre-RFD data presented in the FY 2016 report continued to be grouped with Center-requested consultations (i.e., product classification and jurisdictional requests that originated with the Centers and not with product sponsors). However, responding to Pre-RFDs and Center-requested consultations are two different OCP activities. Therefore, these two different data groups have been independently reported since FY 2017. Center-requested consultations are discussed in the following section.

Table 6. OCP's Pre-RFD Workloads from FY 2017 to FY 2022.

Pre-RFD Assessment Decisions	FY 17	FY 18	FY 19	FY 20	FY 21	FY 22
Combination Product Assessments	44	48	51	47	30	30[12]
Non-Combination Product Assessments	34	28	29	30	15	19[13]
Unclassified Assessments*	0	6	3	2	1	0
Total Pre-RFD Assessments	75	82	83	79	46	49

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

A high percentage of Pre-RFDs cannot be filed because they lack sufficient information needed for FDA to initiate a review. OCP received 106 Pre-RFD submissions in FY 2022. Of the 106 received, 28 Pre-RFD submissions (26%) were complete, 41 Pre-RFD submissions (39%) were reviewed and not accepted due to their lack of sufficient information for OCP to complete an assessment, and 10 Pre-RFD submissions (9%) were withdrawn[14] by the sponsor. The remaining 27 Pre-RFD submissions (25%) received in FY 2022 are under FDA's review, which has continued into FY 2023. Several of these 27 Pre-RFD submissions were impacted by FDA's pending implementation of a federal appellate court's decision in *Genus Med. Techs., LLC v. FDA*, 994 F.3d 631 (D.C. Cir. 2021) and amendment to section 503 of the Federal

[12] One Pre-RFD was for a constituent part of a combination product; the combination product had been classified in an earlier RFD.

[13] One Pre-RFD response yielded classifications and Center assignments for two products.

[14] Prior to withdrawal requests from the sponsors, six Pre-RFDs had not been screened, three Pre-RFDs had been "filed" after screening, and one was "not filed" after screening.

Food, Drug, and Cosmetic Act.[15] In FY 2022, OCP completed the review of 48[16] total Pre-RFDs, of which 28 were received in FY 2022, 18 were received in FY 2021,[17] and two were received in FY 2020.[18] Twenty-nine[19] Pre-RFD assessments (60%) 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 95 days, with a median review time of 58 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; 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 Med. Techs., LLC v. FDA*, 994 F.3d 631 (D.C. Cir. 2021) and amendment to section 503 of the Federal Food, Drug, and Cosmetic Act. The uncertainty from these considerations delayed their evaluation.

[15] On April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit issued the *Genus* decision, holding that FDA cannot classify as a *drug* any product that meets the *device* definition in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). A *Federal Register* notice about this decision, issued in August 2021, is available at https://www.federalregister.gov/public-inspection/2021-16944/request-for-information-genus-medical-technologies-llc-versus-food-and-drug-administration. In addition, section 3621 of the Food and Drug Omnibus Reform Act of 2022 (FDORA) (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.

[16] This number differs from the number of assessments (i.e., 49) in Table 6 because one Pre-RFD submission yielded two classifications and Center assignments.

[17] The initial submissions of the 18 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, nine were accepted for review at the end of FY 2021, and the other nine were accepted for review in FY 2022.

[18] The initial submissions of the two Pre-RFDs received in FY 2020 lacked sufficient information to be accepted by FDA for review. They were finally accepted for review in FY 2021 after several iterations of Additional Information requests had been made to the sponsor.

[19] This number differs from the number of Pre-RFDs received/completed in FY 2022 (i.e., 28) because one Pre-RFD submission yielded two classifications and Center assignments.

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

Classification	Pre-RFDs Issued	Percent Issued in 60 Days
Drug-Device	25	60%
Drug-Biologic	3	67%
Device-Biologic	2	50%
Drug-Device-Biologic	0	N/A
Total	30	60%

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

Center Assignment	Pre-RFDs Issued	Percent Issued in 60 Days
CDER	17	70%
CBER	2	50%
CDRH	11	45%
Total	30	60%

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

Classification	Assignments Issued	Percent Issued in 60 Days
Drug	9	78%
Biologic	1	0%
Device	9	55%
Total	19	63%

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

Center Assignment	Pre-RFDs Issued	Percent Issued in 60 Days
CDER	10	70%
CBER	2	50%
CDRH	7	57%
Total	19	63%

B. OCP's Performance on Internal Center- or Office-Requested Product Classification and Center-Assignment Consultations

In addition to handling RFDs and Pre-RFDs submitted by industry/sponsors, OCP provides classification and Center-assignment feedback for combination and non-combination products in response to requests from FDA's Centers/Offices (i.e., Classification and Center-Assignment Consultations (CCA Consults)). For instance, Centers may contact OCP for assistance in determining whether the combination product submitted to a Center for review is appropriately assigned to that Center or whether the sponsor would need to be referred to OCP for a Pre-RFD/RFD. The number of CCA Consults submitted to OCP is presented in Table 11.

Table 11. Number of CCA Consults by Center from FY 2019 to FY 2022.

Center Assignment	FY 19	FY 20	FY 21	FY 22
CDER	51	44	35	35
CBER	4	4	8	7
CDRH	14	27	23	12
Unassigned*	4	4	33[20]	21
Total	73	79	99	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.

Table 12. Number of OCP's Additional Product Classification and Center-Assignment Activities from FY 2019 to FY 2022.

	FY 19	FY 20[21]	FY 21	FY 22
Jurisdiction/Classification Activities	463	950	375	235

[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.

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

C. OCP's FY 2022 Activities and Accomplishments

Table 13 highlights OCP's Activities for classification and Center-assignment for FY 2022.

Table 13. Specific FY 2022 Activities by OCP.

Type of Activity	FY 2022 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 assignment for challenging categories of products and • Pursue and support related policy initiatives, including (1) clarifying standards for cross-labeled combination product classification and assignment, (2) clarifying the regulatory status of software used with a drug or biological product, (3) determining when container/closures are also considered devices, and (4) classifying articles that meet both the *biological product* and *device* definitions.
Enhancing the timeliness, consistency, and clarity of jurisdictional decisions across FDA	OCP continued to facilitate product classification and jurisdictional meetings with CBER, CDER, CDRH, and OCC staff to exchange information and discuss challenging product classification and assignment issues before FDA.
Developing part 3 regulations	OCP continued to lead efforts to finalize a rule to amend 21 CFR part 3 for clarity and consistency with more recent legislative and policy developments.

III. Combination Product Premarket Review

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

In 2002, FDA established procedures for CBER, CDER, and CDRH staff to follow when requesting, receiving, handling, processing, and tracking inter-Center consults (also referred to as "inter-Center consult requests" in this document). These procedures were formally incorporated into the FDA Staff Manual Guide (SMG) 4101 (titled "Inter-Center Consult Request Process").[22] 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 2022, FDA continued its efforts to improve the inter-Center consult process for combination products, including completing significant updates to the information technology (IT) system. In addition, OCP continued to (1) enhance its monitoring of quantitative metrics on inter-Center consults and (2) solicit qualitative input, including feedback from users via surveys and direct user interactions. These efforts have been used to identify opportunities for improvements in the inter-Center consult process, FDA's IT systems, FDA's staffing utilization, and the resources available to staff, which ultimately ensures an efficient review process and promotes alignment of Agency efforts. OCP also continued to lead 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 2022 by CBER, CDER, and CDRH (including submissions filed or received in FY 2022), as well as the timeliness of these reviews.

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

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

combination products, the Prescription Drug User Fee Act Reauthorization of 2017 (PDUFA VI) goals were referenced for priority and standard new drug applications (NDAs) and applicable biologics license applications (BLAs), the Generic Drug User Fee Amendments (now GDUFA II) goals were referenced for abbreviated new drug applications (ANDAs), and the Biosimilar User Fee Amendments (now BsUFA II) goals were referenced for the biosimilar BLAs. For CBER-led or CDRH-led combination products, Medical Device User Fee Amendments (now MDUFA IV) goals were referenced for expedited and original premarket approval applications (PMAs), premarket notifications (510(k)s), De Novos, and device BLAs.

- Some product review goals, such as for NDAs, are defined by the number of months given to review the product. Due to the differences in the numbers of days in each month (28 to 31), 10 months represents a range from 304 days (such as February 1 to December 1) to 306 days (such as March 15 to January 15), and 6 months represents a range from 182 days (such as February 15 to August 15) to 184 days (such as July 15 to January 15).

- The median review times were based on FDA's first-cycle review performance results for PDUFA VI goals. For MDUFA IV goals, the median review times were based on the total MDUFA IV decision review time. The actual review time was used when only one action was measured.

B. Requirement Workload Trends: FY 2017 to FY 2022

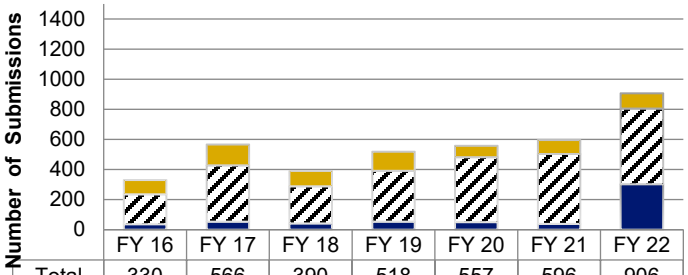
As shown in Table 14, 906 original applications were submitted for review in FY 2022.

Table 14. FY 2017 to FY 2022 Submission Review Workloads.

Submission/Request	FY 17	FY 18	FY 19	FY 20	FY 21	FY 22
Total Combination Products Submitted for Review	566	390	518	557	596	906

As reflected in Table 15, of the original combination product applications received, 56% were received by CDER, 11% were received by CDRH, and 33% 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 16	FY 17	FY 18	FY 19	FY 20	FY 21	FY 22
Total	330	566	390	518	557	596	906
CDRH	95	138	102	126	75	93	101
CDER	199	375	246	339	432	464	503
CBER	36	53	42	53	50	39	302

Table 16 presents the 906 original applications for combination products received in FY 2022, broken down by the identified 10 application types and by the product's initial classification into one of nine categories of combination products.[23] The same table reflecting applications received in FY 2021 has been updated in Appendix A to reflect corrections and actions as of September 30, 2022. The majority of the applications received in FY 2022 were original investigational new drug applications (INDs) (72%), followed by ANDAs (10%). Also, the most common combination product category was the pre-filled biologic delivery device/system (35%).

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

Table 16. Workload by Combination Product Category Number.

Application Type	1	2	3	4	5	6	7	8	9	Total
Original NDA	4	18	0	0	0	0	1	0	2	25
Original BLA	2	1	11	0	0	2	0	0	3	19
Original PMA	0	0	0	2	0	0	0	0	2	4
Original 510(k)	4	1	0	41	0	0	7	1	3	57
Original IND	144	41	307	6	10	46	11	73	16	654
Original Investigational Device Exemption (IDE)	3	1	0	35	4	1	4	1	4	53
Original Humanitarian Device Exemption (HDE)	0	0	0	0	0	0	0	0	0	0
ANDA	13	75	0	0	0	0	0	0	6	94
Biosimilar BLA	0	0	0	0	0	0	0	0	0	0
De Novo	0	0	0	0	0	0	0	0	0	0
Total	170	137	318	84	14	49	23	75	36	906

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.[24]

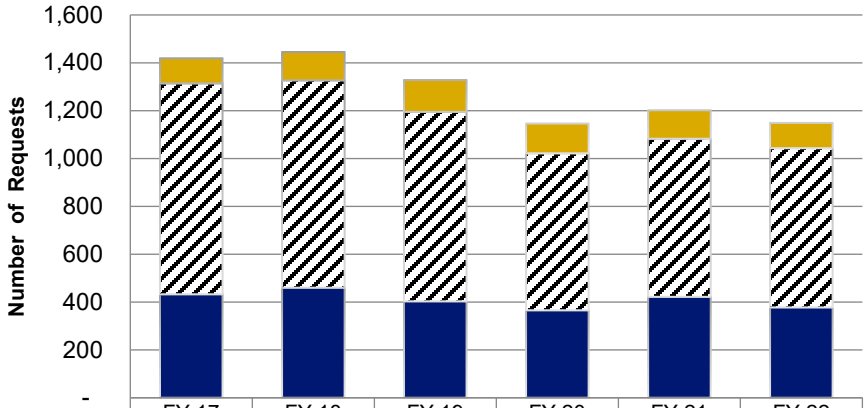
OCP oversees and facilitates coordination among review Centers under the inter-Center consult process to ensure consults are completed in a timely manner. For example, OCP monitors ongoing inter-Center consult requests for correctness (e.g., ensuring the information in the consult requests are complete 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 2022, there were 1,149 inter-Center consults for combination products. Table 17 shows the number of FY 2022 inter-Center consults requested by each Center.

[24] 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.



	FY 17	FY 18	FY 19	FY 20	FY 21	FY 22
Total	1,419	1,445	1,328	1,146	1,202	1,149
CBER	105	118	133	124	119	106
CDER	881	867	792	656	661	665
CDRH	433	460	403	366	422	378

In Table 18, the total number of inter-Center consults in FY 2022 is compared to the previous 5 years.

Table 18. FY 2017 to FY 2022 Inter-Center Consult Workloads.

Submission/Request	FY 17	FY 18	FY 19	FY 20	FY 21	FY 22
Total Inter-Center Consult Requests	1,419	1,445	1,328	1,146	1,202	1,149

In Table 19, the number of inter-Center consult requests during FY 2022 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	Number of Consults
CBER	--	39	66	1	--	106
CDER	18	--	643	--	4	665
CDRH	10	368	--	--	--	378
Total	28	407	710	1	4	1,149

* 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	--	92	--	92
BLA	10	111	--	121
IND/Pre-IND	91	363	--	454
NDA	--	94	--	94
510(k)	--	--	17	17
De Novo	--	--	4	4
IDE	--	--	117	117
PMA	2	--	95	97
Pre-Submission	2	--	145	147
Other**	1	5	--	6
Total	106	665	378	1,149

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

C. Timeliness in Days of the Reviews of Combination Products

FDA is required to report the timeliness of its reviews of combination products. Table 21 summarizes the review types and applicable review performance targets for original NDAs, ANDAs, Prescription Drug User Fee Act BLAs, BsUFA BLAs, PMAs, De Novos, and 510(k)s. PDUFA VI, GDUFA II, BsUFA II, and MDUFA IV established review performance goals for many types of drug, device, and biological product premarket applications. These goals reflect current expectations about the portion of premarket applications that will have an action within a specified time frame. Performance goals apply only to a portion of all applications of a certain type, and they do not require that every application be reviewed in accordance with the applicable timeframe. Typical goals range from 50% to 90% and vary by year.

- For MDUFA IV performance goals, refer to https://www.fda.gov/media/102699/download.
- For PDUFA VI performance goals, refer to https://www.fda.gov/media/99140/download.
- For GDUFA II performance goals, refer to https://www.fda.gov/media/101052/download.
- For BsUFA II performance goals, refer to https://www.fda.gov/media/100573/download.

Table 21. Performance Goals for Original Applications

User Fee Program	Original Application Type	Review Type	Review Goal Within
PDUFA VI	NDAs	Priority	6 Months
PDUFA VI	NDAs	Standard	10 Months
PDUFA VI	BLAs	Priority	6 Months
PDUFA VI	BLAs	Standard	10 Months
MDUFA IV	Expedited and Original PMAs	Standard with No Advisory Committee Input	180 Days
MDUFA IV	Expedited and Original PMAs	Standard with Advisory Committee Input	320 Days
MDUFA IV	510(k)s	Standard	90 Days
MDUFA IV	BLAs	Priority	6 Months
MDUFA IV	BLAs	Standard	10 Months
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 2021 and FY 2022 Review Performance Results," updates FDA's final review performance results on the FY 2021 combination product submissions and presents FDA's preliminary[25] review performance results on the FY 2022 combination product submissions through September 30, 2022.

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

D. FY 2021 and FY 2022 Review Performance Results

Table 22 shows the final[26] FY 2021 review goal performance results. Review goal performance data are based on the fiscal year receipt cohort.

Table 22. Final FY 2021 Review Goal Performance Results.

Original Application Type	Review Type	Review Goal Within	Number of Combination Products	Median or Actual Review Time (Days)	Range of Review Time (Days)
NDAs	Priority	6 Months	13	182	150 to 367
NDAs	Standard	10 Months	28	303	6* to 425
BLAs	Priority	6 Months	3	224	182 to 245
BLAs	Standard	10 Months	6	364	336 to 456
Biosimilar BLAs	Standard	10 Months	1	361	361
Expedited and Original PMAs	Standard	180 or 320 Days	4	178	158 to 266
510(k)s	Standard	90 Days	45	86	0 to 230
De Novos	Standard	150 Days	2	215	198 to 231
ANDAs	Standard	10 Months	84	301	287 to 600
ANDAs	Priority without Pre-Submission Facility Correspondence	10 Months	28	302	287 to 464
ANDAs	Priority with Pre-Submission Facility Correspondence	8 Months	8	240	230 to 331

* 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.

[26] *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 2022 review goal performance results through September 30, 2022.

Table 23. Preliminary 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)
NDAs	Priority	6 Months	6	181	133 to 243
NDAs	Standard	10 Months	8	303	285 to 365
BLAs	Priority	6 Months	1	231	231 to 231
BLAs	Standard	10 Months	3	365	365 to 365
Biosimilar BLAs	Standard	10 Months	0	N/A	N/A
Expedited and Original PMAs	Standard	180 or 320 Days	3	107	90 to 178
510(k)s	Standard	90 Days	48	72	0 to 374
De Novos	Standard	150 Days	0	N/A	N/A
ANDAs	Standard	10 Months	60	301	289 to 424
ANDAs	Priority without Pre-Submission Facility Correspondence	10 Months	51	300	238 to 413
ANDAs	Priority with Pre-Submission Facility Correspondence	8 Months	9	238	226 to 244

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 2017 to FY 2022 are presented in Table 24. In particular, in FY 2022, OCP received 160 requests for product-specific assistance, the responses to which contributed to ensuring the timely, effective, and aligned review of combination products.[27]

Table 24. Number of OCP's Premarket Activities from FY 2017 to FY 2022.

	FY 17	FY 18	FY 19	FY 20	FY 21	FY 22
Premarket Review Activities	525	321	144	188	124	160

Notably, in FY 2022, 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 consistency for when the submissions of two marketing applications for combination products are appropriate;

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

- Clarification for the use of and type of master files; and

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

In addition to addressing these issues, OCP completed the following premarket activities during FY 2022:

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

- OCP hosted premarket meetings with industry to provide clarifications on the proper use of master files for specific combination products; and

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

Examples of these activities are presented in Table 25.

Table 25. Other Significant Premarket Review Facilitation or Assistance Provided by OCP in FY 2022.

Type of Activity	FY 2022 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; • Ophthalmic products in light of *Genus Med. Techs., LLC v. FDA*; • The IND human factors protocol submission process and the review timeline for IND study results; • 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; • Drug-device polymer interactions in implants; • Resolving a disagreement between the review team and the application holder's request that the review team provide more information on how to resolve deficiencies; • The compatibility of needleless syringes with a Luer-activated valve; and • Clarifying what regulatory requirements and premarket review pathways apply to certain products in light of the ruling in *Genus Med. Techs., LLC v. FDA*, which held that products (other than combination products) that meet both the *drug* and the *device* definitions must be regulated as devices.

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 particular, in FY 2022, OCP's postmarket programmatic work included the following:

- Leading or supporting Centers' development of additional guidance on CGMPs;
- Publishing a listing of alternative or streamlined mechanisms for compliance with combination product CGMP requirements as mandated by the Cures Act;
- 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 2022 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 2017 to FY 2022.

	FY 17	FY 18	FY 19	FY 20	FY 21	FY 22
Postmarket Regulatory Activities	74	86	62	113	84	39

OCP engaged in 39 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 stakeholders' 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. 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 2022. Therefore, the percentage is zero of the total combination product submissions (i.e., based on the total number of combination product submissions reported in the "Combination Product Premarket Review" section of this report). Data provided in the "Premarket Review Facilitation/Oversight" section of this report provide examples of OCP's informal facilitation and resolution of issues related to premarket review.

VI. Policy Activities and Accomplishments

OCP's policy activities include leading and contributing to policy initiatives important to the regulation of combination products. Key examples of such activities pursued in FY 2022 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 was involved in the implementation of activities related to PDUFA VI for combination products (e.g., developing bridging and human factors guidance documents).

B. Streamlining Regulations

OCP continued its work on amending FDA's jurisdictional regulations in 21 CFR part 3, including reviewing the comments received on the proposed rule,[29] to update and clarify the regulations in light of legislative and other 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 and (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 2022, OCP led the development and publication of a *Federal Register* notice on alternative or streamlined mechanisms for complying with CGMP requirements for combination products;[30] publication of this notice was mandated by the Cures Act.

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

[30] See 87 FR 56066 (Sep. 13, 2022), available at https://www.govinfo.gov/content/pkg/FR-2022-09-13/pdf/2022-19713.pdf.

In addition, OCP contributed to the development and publication of additional documents implicating the regulation of combination products, including the following:

- Medical Device De Novo Classification Process (final rule) (Oct. 2021);[31]
- COVID-19 Public Health Emergency: Considerations for the Development of COVID-19-Related Sanitation Tunnels for Application of Aerosolized Antiseptics to Humans (final guidance document) (Feb. 2022);[32]
- Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4 Guidance for Industry (final guidance document) (March 2022);[33]
- Current Good Manufacturing Practice, Certification, Postmarketing Safety Reporting, and Labeling Requirements for Certain Medical Gases (proposed rule) (May 2022);[34]
- Risk Management Plans to Mitigate the Potential for Drug Shortages (draft guidance document) (May 2022);[35]
- Patient Labeling for Human Prescription Drug and Biological Products (final guidance document) (July 2022);[36]
- Conducting Remote Regulatory Assessments Questions and Answers (draft guidance document) (July 2022);[37] and
- Clinical Decision Support Software (final guidance document) (Sept. 2022).[38]

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[31] https://www.federalregister.gov/documents/2021/10/05/2021-21677/medical-device-de-novo-classification-process.

[32] https://www.federalregister.gov/documents/2023/03/13/2023-05094/guidance-documents-related-to-coronavirus-disease-2019-covid-19. **Note:** This guidance document is no longer in effect since the expiration of the COVID-19 PHE declaration.

[33] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/certain-ophthalmic-products-policy-regarding-compliance-21-cfr-part-4-guidance-industry.

[34] https://www.federalregister.gov/documents/2022/05/23/2022-10458/current-good-manufacturing-practice-certification-postmarketing-safety-reporting-and-labeling.

[35] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/risk-management-plans-mitigate-potential-drug-shortages.

[36] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/instructions-use-patient-labeling-human-prescription-drug-and-biological-products-content-and-format.

[37] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/conducting-remote-regulatory-assessments-questions-and-answers.

[38] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-decision-support-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 2022; 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 2022 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 RFDs and 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 2022 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 the development of a final guidance document on human factors studies for combination products; • Continued to lead the development of a draft guidance document on the technical aspects of intravaginal system combination products; • Continued to lead 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 a working group on insulin pump labeling; • 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 • Led ongoing efforts to revise the published draft guidance document on postmarket changes for combination products. OCP participated in the development of the following policy documents: • Rulemaking on De Novo classification; • 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;

Type of Activity	FY 2022 Activities
	• Cross-Center draft guidance document on technical considerations for container closures that are also device constituent parts; and • International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use's (ICH's) Q12 implementation guidance document.
Participating in other inter-Center and Agency-wide working groups to clarify issues related to the combined use of medical products	OCP led or participated in working groups with Centers and other Agency components regarding the following: • Non-prescription drug availability; • The Agency's thinking on the regulation of certain software output as drug labeling; • Application of artificial intelligence and machine learning in investigational, diagnostic and treatment settings; • Issues such as importation of prescription drugs, good guidance practices, and enforcement policies; and • Considerations for compounded drugs for use with devices.
Conducting procedural oversight and facilitation and other activities	• OCP led a working group regarding the monitoring and continuous improvement of the inter-Center consult process, including IT developments and enhancements; • OCP continued to chair a cross-Center working group to develop procedures 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 2022 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 a 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. • 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 stakeholders.

- OCP implemented four enhancement releases in FY 2022 to improve the Inter-Center Consult Request workflow and data capture system, including changes to better enable the requesting Center to know to which group they should send a consult request and features to enhance the user experience, such as a new component for downloading the work product provided by the consulted Center.

- OCP implemented eight enhancement releases in FY 2022 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 graphs to enable unique visualization capabilities, redesigning the user interface with modern elements, automating the connection to an existing data source, and reorganizing and adding content based on user feedback.

- OCP implemented four enhancement releases for FY 2022 to improve the electronic system that manages the workflow and data capture system for Pre-RFD and RFD reviews and decisions. Examples of enhancements included adding (1) a new capability to withdraw a previously submitted Pre-RFD or RFD, (2) system-generated notifications to prompt the timely review of submissions, (3) enhanced reporting capabilities, and (4) personalized dashboard views for reviewers. OCP completed a formal pilot with external volunteers of a new Pre-RFD and RFD electronic submission process that was aimed at improving the efficiency and completeness of electronic submissions. Based on feedback received from the pilot, updates were made to the electronic submission process, which is pending release for use.

- OCP provided training, demonstrations, user guides, and other resources to new users from all three human medical product Centers for all OCP-led systems. OCP also engaged users through surveys, user shadowing sessions, 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, the Pharmaceutical Research and Manufacturers of America, and the Biotechnology Innovation Organization) 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 stakeholders and help FDA address questions or challenges faced by sponsors developing combination products.

In addition, 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.

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

In FY 2022, FDA addressed a wide range of topics about which stakeholders had questions, concerns, or proposals for Agency consideration. These topics included emerging issues in combination product regulation and the broader area of 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 stakeholder priorities for further action.

Examples of OCP's FY 2022 outreach activities via industry conferences are included in Table 30.

Table 30. Examples of FY 2022 Outreach Activities.

Type of Activity	FY 2022 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 (AAMI)/FDA/British Standards Institute (BSI) International Conference on Medical Device Standards (Oct. 2021) • Drug Information Association (DIA) Combination Products Conference (Oct. 2021) • Food and Drug Law Institute (FDLI) Combination Products Webinar (Dec. 2021) • Orange County Regulatory Affairs (OCRA)/San Diego Regulatory Affairs Network (SDRAN) Introduction to Combination Products Virtual Event (Dec. 2021) • SMi's Pre-Filled Syringes East Coast (Apr. 2022) • Partnership Opportunities in Drug Delivery (PODD) Combination Product Panel (May 2022) • DIA Annual Conference (June 2022) • The Organisation for Professionals in Regulatory Affairs (TOPRA)/CRED Drug/Device Combination Products Course (June 2022) • Medtech & Pharma Platform (MPP) 2022 Annual Conference (Sept. 2022)

Appendix A: FY 2021 Updated Performance Detail

The table below reflects the 563 original applications classified into one of nine categories of combination products received in FY 2021.

Table 1. Workload by Combination Product Category Number.

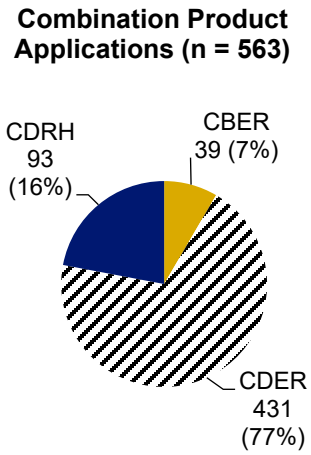
Application Type	1	2	3	4	5	6	7	8	9	Total
Original NDA	13	20	0	1	0	0	0	0	3	37
Original BLA	1	0	10	0	0	0	0	0	2	13
Original PMA	0	0	0	4	0	0	0	0	0	4
Original 510(k)	5	0	1	39	0	0	1	0	0	46
Original IND	14	59	43	4	4	43	8	106	9	290
Original IDE	1	0	0	24	13	0	5	2	6	51
Original HDE	0	0	0	0	0	0	0	0	0	0
Original ANDA	34	79	0	0	0	0	0	0	7	120
Biosimilar BLA	0	0	0	0	0	0	0	0	0	0
De Novo	0	0	0	2	0	0	0	0	0	2
Total	68	158	54	74	17	43	14	108	27	563

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 2021 by Center lead, as of September 30, 2022.



FY

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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