ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4

Journal of Coastal Life Medicine

# Regulatory Prospective about Combination Products in USFDA

**Received:** 26 October 2022, **Revised:** 28 November 2022, **Accepted:** 31 December 2022

[1]Rajole Pratiksha R., [2]Sawant Prerana P., [3]Dhopare Mahesh R., [4]Kashid Girish A.
[1]Student M. Pharm- Drug Regulatory Affairs
Sanjivani College of Pharmaceutical Education and Research.
Kopargaon, Ahmednagar, Maharashtra, India.
Telephone Number: 8007724947
Email id: pratiksharajole2@gmail.com
[2]Student M. Pharm- Drug Regulatory Affairs
Sanjivani College of Pharmaceutical Education and Research.
Kopargaon, Ahmednagar, Maharashtra, India.
Telephone Number: 8369865218
Email id: sawantprerana8@gmail.com
[3]Student M. Pharm- Drug Regulatory Affairs
Sanjivani College of Pharmaceutical Education and Research.
Kopargaon, Ahmednagar, Maharashtra, India.
Telephone Number: 8390606122
Email id: m4maheshdhopare@gmail.com
[4]Head of the Department, Pharmaceutical Chemistry
Sanjivani College of Pharmaceutical Education and Research.
Kopargaon, Ahmednagar, Maharashtra, India.

## Keywords
combination product, RFD, OCP

## Abstract
All healthcare goods in the pharmaceutical sector are classified as Drugs, Devices, and Biologics, and they are governed by their respective regulatory authorities. In the current context, Science and technological advancements have led to the development of innovative novel items in the healthcare sector. More accurate illness identification and treatment, as well as the growth of these revolutionary technologies, have resulted in a blurring of the lines. Due to historical distinctions between healthcare products, these developments gave rise to products with merged features. A regulation about combination products and the FDA's perspective. The article discusses guidelines regarding the combination product and what are the challenges that occur to regulate combination products

**History**

The basic principle of product regulation managed to evolve in the United States in 1990, when the Safe Medical Device Act of 1990 (SMDA) was passed, by trying to amend the FDC Act (Federal Food, Drug and Cosmetics Act). There was no organized regulatory process before that, and these kinds of products are done on a case-by-case basis. There had been a need at the time for a legislative authority to regulate combination products, so the Office of Combination Products (OCP) was formed in 2002, as needed by the Medical Device User Fee and Modernization Act (MDUFMA) of 2002. According to section 503(g) of the act, OCP is willing to take responsibility for the immediate assignment of a refer agency centre that will have primary jurisdiction for the evaluation and supervision of a combination product helping in ensuring prompt and efficient premarket review by monitoring the punctuality and coordinating reviews involving more than one agency centre; ensuring appropriate and effective post-market regulation of combination products, and settling disputes concerning the evaluation and combination products regulations.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

## 1. Introduction

A combination product is defined in 21 CFR 3.2(e) as one that combines a medicine, a device, and/or a biological product. "Constituent parts" of a combination product refers to the medications, devices, and biological products that are a part of the combination product. [3]

A substance made up of more than two regulated components (that is a biologic and a device, a drug, and a device, or a biologic and a drug and a device) that have been linked together, blended, or combined in any other way. [3]

The new biologic-device or drug-device combination product allocated to the CDER or CBER and designated to the drug or biologic product regulatory scheme should adhere to the processes for Investigational New Drug (IND), New Drug Application (NDA) or Biologics Licence Application (BLA), as appropriate. [3]

The Agency center designated as the “lead center" will have main control over a combined product. The lead center for the combination product's premarket review also serves as the center for post-market regulation. [1]

## 2. Methodology

A medication, biological product, or device packaged separately that, according to its investigational plan or proposed labelling, is intended for use only with the approved individually specified drug, biological product, or device where both are necessary to accomplish the indication, intended use, or effect. If that proposed product were approved, the labelling of the approved product would need to be altered.

To address future clinical problems, these products will be combined to treat a wide range of diseases ranging from heart attack and stroke to Alzheimer's, cancer, diabetes, and beyond. In fact, every field of medicine will benefit because disease or injury damage can potentially be erased rather than simply stopped. [4]

Cutting-edge technologies are increasingly being included into combination goods, novel technologies that have great potential for improving patient care. Innovative biological products, drugs, and combination devices have the potential to improve treatment safety and be effective, convenient, and acceptable to patients. Combination items are becoming more popular. being developed to improve the efficacy and safety of standard medical products. The combination products are those in which the components are mixed chemically, physically, or combined in another way like,

- Combination of therapeutic drug and a monoclonal antibody
- A drug or biologic-coated or impregnated device, that is a drug-eluting stent, a catheter with an antimicrobial coating, pacing lead with steroid-coated tip, skin substitutes with cellular components, condom with spermicide, or orthopedic implant with growth factors
- Insulin injector pens, prefilled syringes, metered dose inhalers, and transdermal patches are all available
- A pharmaceutical or biologic product that is packaged with a delivery device
- A surgical tray containing drapes, instruments, and lidocaine or alcohol swabs

### Types of combination products

When evaluating the current process, it became clear that the importance and complexity of issues may vary based on the type of combination product involved. Indeed, a combination product with two clearly distinct components raises very different issues than a combination product manufactured as a unit. As a result, they must be treated differently.

The following categories are derived from the regulations defining combination products:

- Integral combination products: These are the ones in which more than two regulated products joined together as an inseparable single entity. Examples- are prefilled syringes and drug-eluting stents.
- Convenience Kit or Co-Package: First aid or surgical kits containing devices and drugs, biological products, or drug vials bundled with device(s) or accessory kits (auto-injectors, empty syringes, transfer sets).
- Prefilled Drug Delivery Device/ System: Metered-dose inhalers, dry powder inhalers, nasal sprays, pumps, transdermal systems,

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

prefilled iontophoresis systems, or microneedle "patch," among other devices with prefilled medication syringes.

- Device Coated or Otherwise Combined with Biologic: a device scaffold with live cells seeded on it, an extracorporeal column with protein bound to it, or both.[10]

## The Inter-center Agreements

Center for Biologic Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), and Center for Drug Evaluation and Research (CDER) signed three Inter Center Agreements (ICAs) in 1991: Those inter-center agreements between CDRH and CBER, CBER and CDER, & CDRH and CDER.

The following are some examples of major provisions of the CBER-CDRH ICA;

1. Identification of medical devices for which CBER will be the primary regulatory authority.

2. Identifying the devices which will be regulated by CBER under the provisions of the Public Health Services Act (PHSA).

3. The primary mode of action is used to determine the center of primary jurisdiction.

## Regulations in the USA

A combination product is given to an Agency center that will be in charge of regulating it on a lead basis, or with primary authority. According to section 503(g)(1), the combination product's assignment to a lead centre is based on the identification of the constituent portion that contributes to the primary mode of action (PMOA) of the combination product [4]

OCP must assign premarket review duties as per the products PMOA for combination products. By submitting an RFD, a firm may request a formal FDA determination regarding a combination product PMOA and assignment of the lead centre for premarket review and regulation.

Within 60 days after filing the RFD, FDA will end up making a jurisdictional determination, if not then the sponsor's selection of the primary jurisdiction centre will become the assigned centre.[9]

## Primary Mode of Action (PMOA)

The FDA defines the mode of action as the process by which a product achieves its intended therapeutic effect, with "therapeutic" action or effect referring to any effect or action of a combination product that is intended to diagnose, cure, mitigate, treat, or prevent disease, or to affect the structure or function of the body.

The FDA allocates combination product submissions to one of the following centres, which serves as the lead center, based on the primary mode of action (PMOA) of the product:

CDER: Center for Drug Evaluation and Research

CBER: Center for Biologics Evaluation and Research

CDRH: Center for Devices and Radiological Health [3]

The combination product's most significant therapeutic effect is provided by its one mode of action, known as the Primary MOA. The regulator, sponsor, and developer must conduct scientific assessments for the PMOA to be valid. [3]

If the PMOA of a device biological product or combination product is attributable to the biological product, for instance, the centre in charge of premarket review of such a biological product would have primary jurisdiction for the legislation of the combination product. [4]

As a result, the initial most significant therapeutic activity of a combination product is described in the Legal Authorization PMOA as "the single mode of action of a combination". The one action that is intended to make the greatest ability to contribute to the product's overall meant therapeutic effects is the most important therapeutic action. The majority of drug delivery systems of combination products include both a device and a drug. They could simply be a syringe, containing a drug or a complex iontophoresis patch for drug administration. Typically, the therapeutic effect of such a product is significant due to the drug component's role in treating a disease, and the device plays an important role, a secondary role in drug delivery. With CDRH advice, the CDER assesses a variety of products based on their device features.

## Pre-RFD

Pre-RFDs are concise written submissions that a sponsor can submit to OCP to request the FDA's preliminary, nonbinding evaluation of the

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

regulatory identity or classification of a product as a drug, biological product, device, or combination product. Depending on the details contained in a specific Pre-RFD, OCP will offer a written preliminary categorization and/or jurisdictional evaluation of the product.[9]

Any time during the development of a medicinal product, a pre-RFD may be presented.

When determining whether a medicinal product is a medication, device, combination product, or biological product, as well as the center to which it would be allocated, the Pre-RFD procedure is accessible to offer informal, non-binding comments.[7]

Part 3 of 21 CFR contains the RFD process regulations. The following actions have to be followed by a corporation once it has decided to submit a formal RFD to OCP:

- Sponsor RFD preparation and submission.
- FDA notifies the sponsor within five days of receipt that the RFD has been filed or has not been filed.
- Within 60 days of filing, FDA will conduct a technical review and issue a designation letter.
- By 21 CFR 10.75, the sponsor may appeal the RFD judgment if they disagree with it.[9]

## Request for Designation

When the combination product is approved, the sponsor or manufacturer must submit an RFD to the OCP to determine which FDA center will be in charge of the product's evaluation and regulatory process.

Regulatory identity questions, such as whether a product is a medicine, biological product, device, or combination product, are frequently asked in RFDs. Additionally, they could request details about the FDA division that will regulate the product, if it is not a combination product, or about which Agency Center will have primary jurisdiction over its premarket review and legislation. A request letter from the applicant is another name for an RFD. It is an OCP submission in writing. Every product does not require an RFD to be submitted. [6]

## Combination Products Regulations In The Premarket Essentials

A sponsor may decide to submit different applications for the various component of a combination product unless FDA determines that a single application is necessary, according to Sections 503(g)(1)(B) and 503(g)(6) of the Food Drug &Cosmetic Act. When appropriate, FDA will handle the premarket evaluation of any combination product under a single application. [4] The marketing application type filed (a PMA, De Novo, or 510(k) for a device-led combination product; a BLA for a biologic-led combination product; an NDA or ANDA for a drug-led combination product;) should typically be the same as the combination product's Primary mode of Action.

The FDA reviews the combination product as a whole and in addition each of its component parts to determine what is required to illustrate the combination product's safety and effectiveness, weighing the questions and considerations reflected in the statutory and regulatory provisions associated with each constituent part.

Example:

Nonclinical pharmacology and toxicology, clinical pharmacology data, and chemistry, manufacturing, and controls (CMC) information are necessary for a device-led combination product that has been reviewed in an appropriate device application and contains a drug component element.

Engineering, biocompatibility, performance, and other design validation data are often necessary for a combination product which is not device-led and contains a device constituent part. [4]

## Premarket Pathways

A. Device-led combination products:
   1. Premarket Approval (PMA) Applications
   2. De Novo Classification Requests
   3. Premarket Notification (510(k)) Submissions

B. Drug-led combination products:
   1. New Drug Application (NDA)
   2. Abbreviated New Drug Application (ANDA)

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

C. Biologic-led combination products:
1. Biologics License Applications (BLAs) Submitted under Section 351(a)
2. BLAs for Biosimilar and Interchangeable Biological Products Submitted under Section 351(k) [4]

## Product Approval Procedure

The product developer can approach the lead centre for market authorization after the lead center has been assigned by submitting the necessary market application. For a drug product, CDER is designated as the lead centre, and the product is submitted under an NDA. In contrast, a biologic product's lead centre is CBER, and the product is submitted under a BLA. If a device product exists, the lead centre is CDRH, and the product is submitted under either a 510(k) or a PMA, based on the device's classification.

## GMP Considerations

The current GMP for combination products will be considered as the quality system regulations of a combination product. The quality system regulation is mentioned in 210, 211 part of 21 CFR that applies to Drugs and biologics and is commonly known as cGMP. The quality system regulations are given in the 21 CFR 820 that applies to medical Devices and is known as the QSR. The cGMP and QSR legislations are also referred to as predicate rules. Algorithm for assigning lead center to regulate Combination Products.

## Considerations for Post-Marketing

Planning for Post marketing regulatory compliance should therefore include continuing GMP requirements, adverse event reporting, and post-marketing commitments related to a product's specific marketing approval or clearance. Combination products must meet the same post-marketing regulatory requirements as their constituents.

21 CFR Subpart B involves Reporting of Post-Marketing Safety related to the combination products. The Electronic Medical Device Reporting System (eMDR), the Vaccine Adverse Event Reporting System (VAERS), and the FDA Adverse Event Reporting System (FAERS) have all been updated to address combination product reporting considerations. This involves providing applicants for combination products with the option to fulfil various reporting requirements in a single report. [8]

## User Fees

The price associated with the type of application necessary for the product's premarket approval, clearance, or licensure is appropriate for combination products that include a device component, such as drug-device or biologic-device products.

For instance, under MDUFMA, a biologic-device or device-drug combination product for which a PMA is required should pay the PMA charge, while a biologic-device or device-drug combination product for which a 510(k) is required should pay the 510(k) fee. If the FDA demanded two different applications for a combination product, two application fees would be assessed. Sponsors may be eligible for any current waivers or discounts under PDUFA or MDUFMA. [5]

## Combination products examples

Single-entity combination products

- Monoclonal antibody combined with a therapeutic drug
- Prefilled drug delivery systems
- Device coated or impregnated with a drug or biologic

Co-packaged combination products

- Drug or vaccine vial packaged with a delivery device
- First-aid kits containing devices (bandages, gauze), and drugs
- Surgical tray with surgical instruments, drapes, and anaesthetic or antimicrobial swabs

Cross-labelled combination products

- Photosensitizing drug and activating laser/light source [7]

## 3. Discussion

A review article on the regulatory perspective of combination products in the USFDA would provide an overview of the current regulatory landscape and highlight key considerations for manufacturers seeking to develop and market these products. This

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

article could cover several key areas, including the definition and classification of combination products, the regulatory pathways available for these products, and the challenges and opportunities associated with their development and approval. One important area to explore in such an article would be the different types of combination products that exist and how they are classified by the FDA. There are three primary categories of combination products: drug-device, biologic-device, and drug-biologic. Understanding the classification of a particular combination product is critical for determining the appropriate regulatory pathway for its approval.

## 4. Conclusion

Combination products will become increasingly important for pharmaceutical and medical device companies as they seek to extend the life cycle of off-patent medicines. The medical device, biopharmaceutical, and digital health industries continue to prioritize innovation in combination products. Furthermore, US regulations for combination products were developed to alleviate difficulties in the product jurisdiction of combination products in which any of the three centers CDER, CDRH, CBER. The article covers regulations for combination products in the US that will help you to understand the procedure for submission.

## References

[1] Requesting FDA feedback on combination products. FDA. s.l.: U.S department of health and human serices, 2020.
[2] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=3.2
[3] Uemura N, Kasanuki H, Umezu M. New Visualization Models of Designation Pathway and Group Categorization of Device-Drug and Device-Biologic Combination Products Classification in the United States: Analysis of FDA Capsular Decisions. Ther Innov Regul Sci. 2021 Jul;55(4):807-817. doi: 10.1007/s43441-021-00276-x. Epub 2021 Apr 12. PMID: 33844189; PMCID: PMC8238755.
[4] Principles of Premarket Pathways for Combination Products
[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-premarket-pathways-combination-products
[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/application-user-fees-combination-products#userfees
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/how-write-request-designation-rfd
[8] https://www.fda.gov/combination-products/about-combination-products/frequently-asked-questions-about-combination-products#examples
[9] Post marketing safety reporting for combination products https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products
[10] How to request Pre-RFD
[11] https://www.fda.gov/media/102706/download
[12] https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types