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Comparison of Combination Product Regulations: Challenges and approval pathway in the US and Europe

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ABSTRACT

A complex regulatory issue related to the combination products, which combine drugs, device, or biologics, is found in the United States (US) and the European Union (EU). In this review, this paper compares their unique regulatory systems that involve, among other things, classification and approval channels. The Office of Combination Products (OCP) at the FDA regulates in the US based on Primary Mode of Action (PMOA), whereas in the EU, there is not a single definition but on the Medical Device Regulation (MDR), Medicinal Products Directive, frequently a Notified Body Opinion (NBOp) is required, under MDR Article 117. Though their products present greater therapeutic efficacy and patient adherence, there are obstacles such as PMOA determination, intercenter cross-coordination, and Notified Body capacity which present challenges to the products. Subsequent regulatory development should aim at harmonization, integration of digital health, real-world evidence and possible EU centralization as a way to simplify development and make it safe.

INTRODUCTION

In modern pharmaceutical innovation, the popularity of combination products that encompass at least two regulated items, such as drugs, devices, or biologics, has increased. Such a hybrid nature and the need of being able to cope with various regulatory regimes produce unique logistics and legal challenges. In the United States, the statutory definition of a combination product is 21 CFR 3.2(e), and it is regulated mainly by the Food and Drug Administration (FDA) Office of Combination Products (OCP). The agency regulates toward that end in large part by considering the so-called Primary Mode of Action(PMOA) and assigning jurisdiction to one of CDER, CBER, or CDRH, as well as managing inter-unit reviews of those issues. Authorization pathways follow traditional medicinal (NDA or BLA), biological (BLA), or device procedures (PMA), and surveillance after marketing is conducted as per 21 CFR Part 4.(1,2)

In contrast, the European Union does not have a single legal definition of combination products, which is possible because either the Medical Device Regulation (MDR 2017/745) or the Medicinal Products Directive (2001/83/EC), applicable depending on PMOA, provides authority. Notified Bodies and the EMA play primary roles in communicating conformity requirements. Under Article 117 of the MDR, a Notified Body Opinion (NBOp) is required to be submitted to prove device conformity in the case of an integral drug unit.(1,3)

HEALTHCARE IMPLICATION OF COMBINATION PRODUCTS

1. Enhanced Therapeutic Efficacy

The combination products are a pharmaceutical approach of combining two or more treatment modalities, drug, device, or biologic modalities that have been combined leading to maximization of therapeutic benefit. Such studies may be exemplified by drug eluting stents, where pharmacologic agent is delivered directly to vessel wall, and inhalers, where therapeutic agent is deposited right at a target area within the respiratory system. These strategies increase the therapeutic specificity as well as minimize systemic activity.(4)

2. Improved Patient Adherence and Compliance

Fixed-Dose Combinations (FDCs) facilitate the complexity of doses, and simplify the pill burden, thus enhancing patient adherence of drugs, especially in chronic illnesses.(5)

3. Cost-Effectiveness and Operational Efficiency

With the addition or subtraction of several more treatments, the therapeutic effect becomes more convenient, more compliant, and more effective than the individual treatments; this reduces treatment complications and unplanned hospital stays.

4. Innovation in Personalized & Targeted Therapies

Drug-device integration - the combination of pharmacotherapeutics and medical devices - is a central part of the current approaches to personalized medicine allowing to develop interventions that can become dosing-adaptive to real-

time physiological events. Examples of representative cases are the implantable insulin pumps and the self-administration insulin patches that have a continuous glucose monitoring operation.

5. Regulatory Encouragement for Development

Regulatory agencies in particular, the US Food and Drug Administration (FDA) encourages innovation in combination products through a defined existence of designated pathways under 21 CFR Part 3 and 4; creating a safe, and more effective process of gaining approval.

COMBINATION PRODUCT REGULATION IN THE US

Definition:

Combination products, in the United States, are regulated under 21 CFR 3.2(e) and refers to therapeutic or diagnostic products that include multiple classes of medical components- drugs, devices and/or biologics.(6–8)

such combination products can be either of the following types:

1. Physically or chemically fused into the same structure (e.g. drug-eluting stents),
2. Closely bundled (e.g. pre-filled syringes), or
3. Packaged and distributed separately yet to be used at the same time (e.g. injector and a drug which was labeled to be used simultaneously).

Figure: 1

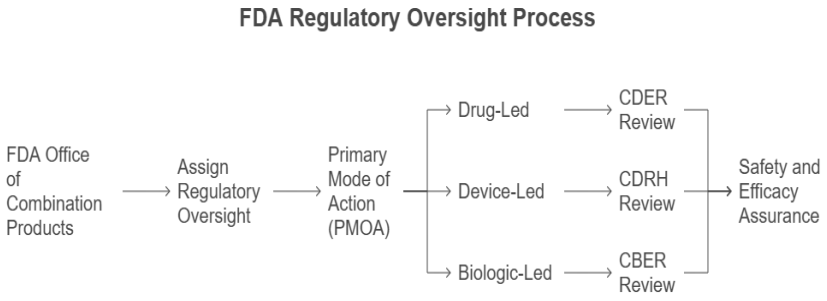


Table: 1

Center	Primary Responsibility
CDER	Controls prescription and the non-prescription of drugs, both small molecule drug constituents
CBER	Controls biological products that include vaccines
CDRH	Regulates the radiation emitting electronic products.

Combination Product Types: USFDA Table: 2

Type	Category	Illustrative Examples
1	Kits and Co-Packaged Assemblies	Device and drug/biologic packaged together, such as surgical or emergency kits, syringes with drug vials, transfer sets.
2	Prefilled Drug Delivery Systems	Devices containing drug formulations, e.g. transdermal patches,nasal sprays.
3	Prefilled Biologic Delivery Systems	Prefilled syringes or pens with biologics like vaccines or monoclonal antibodies.
4	Drug-Integrated or Surface-Treated Devices	Devices embedded or coated with drugs, such as drug-eluting stents, medicated contact lenses, sensor-equipped pills.
5	Devices Incorporating Biologic Entities	Scaffolds embedded with live cells, or extracorporeal devices with immobilized proteins for targeted effects.
6	Conjugated Drug–Biologic Combinations	Antibody–drug conjugates or stem/progenitor cells formulated with drugs for enhanced targeting or therapeutic activity.
7	Separate Products with Coordinated Labeling	Drugs or biologics requiring a companion device (e.g., laser-activated treatments) that are not sold as a single unit.
8	Developmental Products with Potential Cross-Labeling	Drug-device pairings still under evaluation for regulatory linkage, where labeling interdependence is yet to be determined.
9	Fully Integrated Combination Products	Single products combining drug, device, and biologic—such as prefilled syringes containing a biologic-drug conjugate.

Applications for combination products according to PMOA and their review period.

Table: 3

Lead center	Application type	Review period
Center for Drug Evaluation and Research	New Drug Application	6 Months (Priority review)
Center for Biologics Evaluation and	Biologic License Application	10 Months (standard review)
Center for Device and Radiological Health	Humanitarian Device exemption 510 Pre-market	75 Days 90 Days 180 Days

Combination product guidance documents of US FDA.

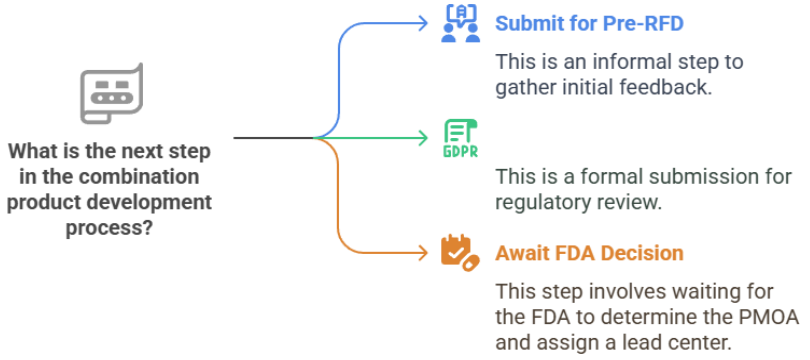
Table: 4

Guidance documents	URL

21 CFR Part 3-Regulation of Combination Products	https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-3
21 CFR Part 4 – cGMP Requirements for Combination Products	https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-4
Post marketing Safety Reporting for Combination Products Guidance for Industry and FDA Staff	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarketing-safety-reporting-combination-products

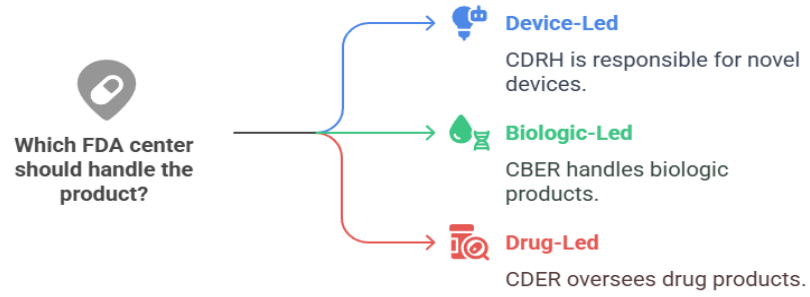
An Overview of FDA Regulatory Pathway of Combination Products

Figure: 2

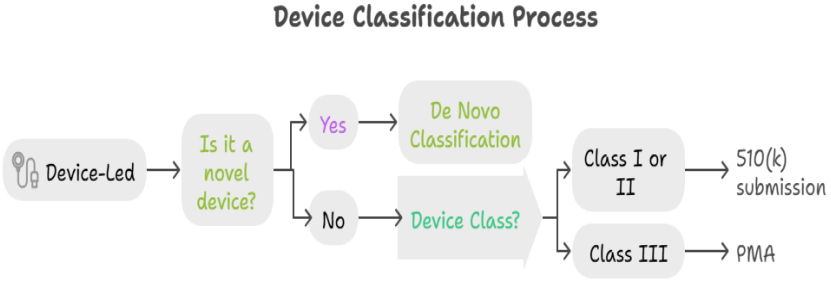


FDA OCP Assigns Review Center

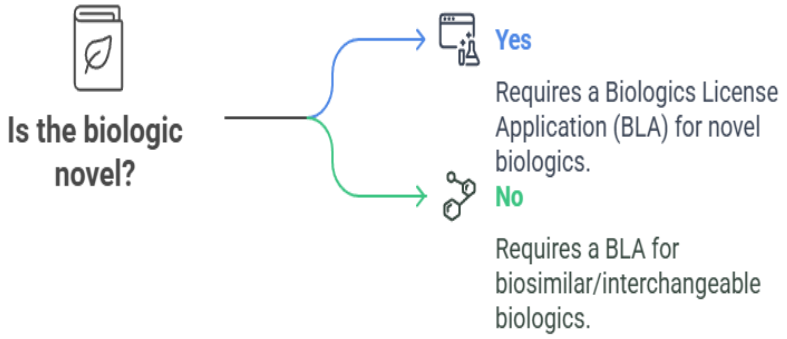
Figure: 3



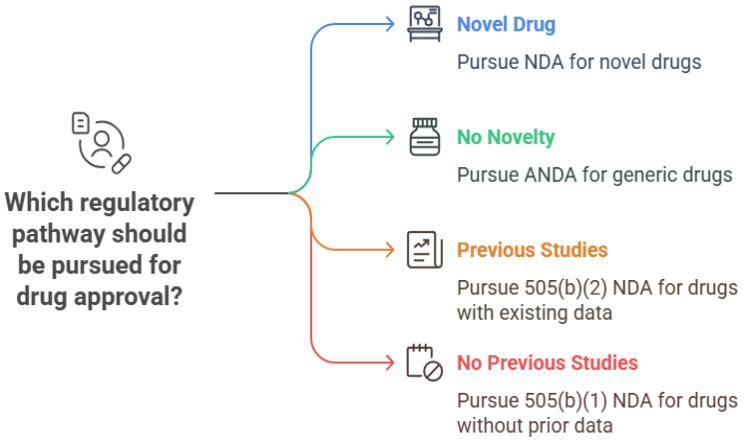
Determination of Regulatory Pathway (on the basis of Novelty)
Device - led **Figure: 4**



Biologic - led **Figure: 5**



Drug - Led **Figure: 6**



Combination product regulation in the European Union (EU)

Combination products in the European Union are regulated based on their primary mode of action (PMOA), are subject to the Medical Device Regulation (1990s-2017/745) when the PMOA is therapeutic, and the Medicinal Products Directive (2001/83/EC) when the PMOA is diagnostic.(3,9)

As opposed to the U.S., there is no single definition of combination products in the EU.

The EU regulation regarding medical devices makes provisions on two types of combination products, which include

(i) drug-device combinations and

(ii) devices with ancillary medicinal substances.(3,9)

When the therapeutic effect is determined by the active pharmaceutical ingredient, the drug-device combinations are regulated as **medicinal products**;

where the therapeutic effect is determined by the device, the product is classed as a **medical device**. However, as devices are defined as incorporating ancillary medicinal substance, consideration must be given to whether a product using the device definition fits and can be classed as a medicinal product prior to consultation with EMA.(9)

Regulatory control will be comprised of Notified Bodies (NBs) on components of the device, and the European Medicines Agency (EMA) to medicinal parts. In the case of integral drug-device products, Article 117 of the MDR ensures Notified Body Opinion (NBOp) to show that safety and performance of such devices meet the required standards.(EY (2024). Navigating EU Regulations for Drug-device Combination Products., n.d.; Pharmavibes (2024). The Importance of Article 117 of the MDR, n.d.)

The role of the Notified Bodies (NBs) in Marketing Authorization Applications (MMA)

The Notified Bodies (NBs) in the European Union (EU) play a central role in the regulatory evaluation of the drug-device combination products, especially within the Marketing Authorization Applications (MAAs). In case, a medicinal product has a device feature that has not been assessed and labeled in CE, an applicant should secure a Notified Body Opinion (NBOp), as stated by Article 117 of Regulation (EU) 2017/745 (MDR). This view ascertains that the element of the device meets the General Safety and Performance Requirements (GSPRs), laid out in Annex I of the MDR, which contributes to the overall benefit to the risk profile of the medicinal product.Technical documentation regarding design, risk management, usability, bio compatibility and sterilization, are also evaluated by the NB. The outcome of the NBOp is filed with the MAA to European Medicines Agency (EMA) or national competent authorities. Such a process is so that the integrated device qualifies in standard set safety and performance levels.The changing complexity of combination products particularly since digital components have increased, impose greater pressure on NBs. Lack of capacity and a changing interpretation of regulatory expectations are some of the challenges that demonstrate the necessity of early participation and understanding between an applicant, NBs and a regulatory agency to allow timely access to the market.

Limitations in Notified Bodies

With the increase in requirements of the MDR, the number of NBs and their scope will decrease. The available number of NBs qualified to assess DDCs may be lower than expected and this can turn out to be challenging for pharmaceutical manufacturers. The expectations regarding the presentation of data showing compliance with the

GSPRs are not yet well defined. The assessment report of the NB, concluding the requested opinion, should be designed in a way that the medicine's competent authority can rely on it for the final marketing authorization (MA). Hence, representatives of the NB and EMA should discuss the expectations and requirements in advance to ensure a consistent procedure.(3,9,12)

Regulatory Examples of Combination Products in EU. **Table: 5**

Items	Examples
Medical devices with an ancillary medicinal substance	Drug-eluting stents Antibiotic-loaded bone cements Haemostatic Medicated condoms Drug-impregnated dressings
Drug- device combinations Integral Non- Integral	 Levonogestrel Non-refillable inhalers Pre-filled syringes Transdermal patches Intrathecal pumps Reusable inhalers Insulin pumps

Certification procedure for MD under the new MDR

Combination products in the EU are not regulated as unique categories. Instead, the applicable framework depends on the product's **PMOA:**

- Medicinal product as PMOA → regulated under Directive 2001/83/EC (Medicinal Products Directive)
- Medical device as PMOA → regulated under MDR 2017/745

This creates two major pathways.(3,9)

1. Drug-Led Combination Products (Medicinal Product with Integral Device)

Examples: Prefilled syringes, autoinjectors, inhalers

Certification Route:

Regulated primarily as a medicinal product.

A Marketing Authorization Application (MAA) is submitted to the EMA or a National Competent Authority.

MDR Article 117 applies as follows:

If the product includes a device component that is not CE marked and is integral to the product, the manufacturer must submit a Notified Body Opinion (NBOp). The NBOp confirms conformity with Annex I – General Safety and Performance Requirements (GSPRs) of the MDR.(3)

Guidance documents: Table: 6

Key Requirements:

- Technical documentation for the device
- Usability and performance testing
- Risk management and benefit-risk assessment

2. Device-Led Combination Products with Ancillary Medicinal Substance

Examples: Drug-eluting stents, bone grafts with antibiotics

Certification Route:

Regulated as a medical device under the MDR.

The device includes a medicinal substance (that supports the device's function but is not the main action).

The manufacturer must apply for a CE marking through a Notified Body.(3,12)

EMA Consultation:

- For Class III or Class IIb devices that administer a medicinal product, the Notified Body must consult the EMA or NCA regarding the medicinal component.
- The EMA assesses the quality, safety, and usefulness of a substance within a combination.(12)

Guidance / Regulation	URL
MDR 2017/745	EUR-Lex MDR Regulation
Directive2001/83/EC	EUR-Lex 2001/83
MDCG 2021-24 (Article 117 Guidance)	Download PDF
EMA MDR Resource Page	EMA & MDR

Post-Market Requirements

Table: 7 US

Requirement Type	Description	Reporting Timeline
5-Day Reports	Cases of events wherein remedial actions are necessary to avert risk of death/severe injury	Within 5 working days
MDR Reports	Medical Device Reporting under 21 CFR 803 (death, injury and malfunction)	30 calendar days
ADE/AE Reports	21 CFR 314.80 / 600.80 Adverse Drug or Biologic Experience reports	15 calendar days (serious)
Field Alerts	Drug products challenges that affect quality of labeling (per 21 CFR 314.81)	ASAP, not more than 3 working days
Periodic Reports	Combination product PMS reports or summaries (PSURs, PADERs)	Quarterly,

Table: 8 EU

Requirement	Summary
PMS & Vigilance	MDR Chapter VII: PMS plans, Periodic Safety Update Reports must be followed
UDI System	The component of the devices should satisfy the Unique Device Identification of MDR
Incident Reporting	Via EUDAMED and national competent authorities
Change Management	Changes to the device or drug part may trigger reassessment

Reasons for Recalls in Combination Products

I. **Manufacturing-Related Issues**
Incomplete manufacturing is still the main reason behind combination products recalls. These are microbial contamination, chemical instability, and particulate matter observed in sterility assurance testing. In the U.S., such issues comprised nearly 37 percent of any drug-relate recalls during the period between 2018 and 2022.(13)

II. **Labeling & Packaging Defects**
Mislabeling can be fatal because it may include wrong dosage or names of drugs, as well as lead to huge recalls. Poorly packaged, which cannot guarantee the preservation of sterility or appropriate administration of effective dosages may also result in regulatory steps.(14)

III. **Device or Software Malfunctions**
Numerous recalls are the fault of mechanical components or software components in combination products. These are defective injector springs, and bad infusion pumps. Software bugs can cause dose errors and cause device malfunction in the context of smart drug delivery systems.(15)

IV. **Impurities and Potency Failures**
Genotoxic impurities in drugs, e.g. nitrosamines, and divergence in potency in batches of drugs has resulted in high profile recalls. One of the most popular examples is the common recall of valsartan and metformin, which was affected by the presence of nitrosamines in them.

V. **Post-Marketing Adverse Events**
An adverse event unexpectedly detected via post-market surveillance systems, including those of the FDA, the MAUDE and the FAERS databases, usually serves as a warning that a voluntary or even mandated recall is in order. These are allergic reactions, unfavorable results of treatment and device failures that go unplanned.

Regulatory Challenges for Combination Products

United States (US)

Combination products in the United States are coded in 21 CFR 3.2(e) and the Office of Combination Products in the Food and Drug Administration (FDA) is their regulating authority. Yet, there are quite a number of challenges.(16)

Key challenges include:

PMOA Determination
The identification of the Primary Mode of Action (PMOA) is very challenging especially in a case where a product is composed of a drug and device and software. This sort of ambiguousness makes classification difficult and delays the review.(13,17)

Intercenter Coordination
Similar to combination products, concurrent-filed combination products can result in intercenter consultation among the three FDA centers of CDER, CBER, and CDRH, and as such extend the timeline and change review expectations.(13)

GMP Compliance
Section 21 of the Code of Federal Regulations, part 4, thereby provides GMPs to both drugs and devices, thereby bringing to the manufacturer two obligations of compliance and the possibility of overlapping inspections.

Post-market surveillance complexity
Strictness of the post-market reporting schedules and their diverse formats (e.g. FAERS and MAUDE) pose compliance issues especially when it comes to single-entity products.

European Union (EU)

EU does not have a harmonized or common definition of combination products. Regulation is rooted on PMOA through either Directive 2001/83/EC Medicinal Product Powered by EUR-Lex

Medical Device regulated by MDR 2017/745

Key challenges include:

Fragmented Regulatory Pathways
Dual legislation in the EU, as opposed to the U.S., collates into disintegrated pathways. In the case of drug-device products both EMA and Notified Bodies (NB) reviews are mandatory.(18)

NB Opinion under MDR Article 117
Such products as prefilled syringes would need NB Opinion (NBOp) where the device element is not CE marked, which further complicates things and introduces delays.(19)

NB Capacity Constraints
In the wake of the introduction of the Medical Device Regulation (MDR), there has been a decrease in the total number of Notified Bodies (NBs) which in turn has led to the availability of fewer resources of Notified Bodies in terms regulating the evaluation of devices. gadgets.(20)

CONCLUSION

Regulatory provisions of combination products in the European Union and the United States of America offer opportunities as well as problems to pharmaceutical innovation. The U.S has such definition and regulatory framework, commonly described as the combined products within the Office of Combined Products of FDA, whereas the EU is in more fragmented, as the entity to be regulated depends on the Primary Mode of Action of the product. The two areas can benefit greatly in the area of combination products in terms of improving therapeutic efficacy, patient adherence, cost-effectiveness, and the development of personalized medicine. Nevertheless, the manufactures encounter tricky regulatory barriers, including identifying the Primary Mode of Action, enabling intercenter coordination, and satisfying a wide variety of quality requirements. The main problems in the U.S. consist in PMOA determination, coordination between the centers, and GMP compliance of the drug and device components. All these concerns the EU with fragmented regulatory pathways, which pose a problem as they need to be provided with a Notified Body Opinion pursuant to MDR Article 117, as well as There are capacity issues among the Notified Bodies.

In the future, the development of regulations will probably revolve around working on harmonization between the FDA and EMA, digital health and AI, the greater utilization of real-world evidence, and possible EU centralization of combination products processes. These developments will help to simplify the regulatory procedure and remain with high standards of safety and efficacy out of these.

Since combination products are growing to become a key factor in healthcare development, further cooperation between regulatory agencies, manufacturers, and clinical institutions will be necessary to resolve existing issues and meet the requirements of new solutions and treatment methods.

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