ClinChoice

eBook

CONSIDERATIONS FOR COMBINATION PRODUCT REGISTRATIONS IN THE U.S. AND THE EU

Authors

Sarita Ranjan, Ph.D, MBA, Senior Manager, Technical Writing
Pravalika Bangunde, M.Sc. , Specialist, Technical Writer

Contributors

Lakshmipriya Kumar, Doctor of Pharmacy, Director, Medical Devices, Medical Affairs
Alma Relja, RAC, CQIA. Director, Regulatory Affairs
Joy Coraza, M.S, Associate Director, Regulatory Affairs
Azher Sharif, PharmD, Medical Writer

Table of Contents

Disclaimer

The information presented in this paper is based on our current understanding of the US and EU regulatory requirements for Combination Products at the time of publishing and is subject to change in the continuously evolving regulatory landscape. Examples provided in this paper are intended for clarification purposes only and may be classified differently depending on their respective design, features, and functionality.

FDA Categories for Combination Products

Figure 1: Possible Constituent Parts of Combination Products

Combination Products are medical products comprised of two or more differently regulated constituent parts. They have many types of usage. For instance, some drug-device combinations, such as metered-dose inhalers, are used to ensure the proper dosage of self-administrated medicines outside the clinical environment. The constituent parts of the Combination Products can be combined in different ways. The intended use of the final combination product leads to varying categorizations in different regulatory regions **(Table 1).**

Table 1: Definition and Categories of Combination Products in the US and the EU jurisdictions

Terminology	US FDA[ii]	EU[i]
Brief summary of definitions	According to Section 503(g) of the FD&C Act and 21 CFR 3.2 (e), a Combination product is a product that is composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. Biological products may include human cells, tissues, and cellular-tissue-based products (HCT/P).	According to EU MDR 2017/745, Combination Products combine a medicinal product or substance and a medical device.

Terminology	US FDA[ii]	EU[i]
Categories	Single-entity, Co-packaged, and Cross-labelled 21 CFR 3.2(e)(1)(2)(3)(4)	Integral, Co-packed, and Referenced MDR Article 1 (8)(9)(10)
Single Entity vs. Integral	A Combination Product has two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity. Examples: A drug-eluting stent, a catheter with anti-microbial coating, a monoclonal antibody combined with a drug, a condom with spermicide, and a pre-filled insulin injector pen.	Devices that, when placed on the market, incorporate, as an integral part, a substance that, if used separately, would be considered a medicinal product. Example: drug-eluting stent. Also, devices intended to administer a medicinal product, where the device and the medicinal product are placed on the market in such a way that they form a single integral product intended exclusively for use in the given combination and which is not reusable. Examples: Single-use pre-filled injectors, drug-releasing intra-uterine devices, and dry-powder inhalers which cannot be refilled.
Co-Packaged	Co-Packaged Combination Products are two or more separate products (drug/device, device/biologic, or drug/biologic) packaged together in a single package or as a unit.	If a medicinal product and a medical device are packed together into a single pack, it is called Co-Packaged. Example: Spoons/syringes packaged with medicine

Terminology	US FDA[ii]	EU[i]
	Example: Drug or vaccine vial packaged with a delivery device, first-aid kits containing drugs (antibiotic ointments, pain relievers, etc.), and devices (bandages, gauge, etc.)	for the administration of that medicine.
Cross-labeled vs. Referenced	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. Example: To reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose. Also, any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect. Example: Photosensitizing drug and activating light source/laser.	Medicinal products, where the product information refers to a specific medical device to be used with the medicinal product, and the medical device is obtained separately by the user of the medicinal product, it is called as referenced. Example: Refillable/reusable injector referenced to be used with insulin.

As shown in **Table 1,** the description of Combination Products is not as elaborate in the EU regulation as in the US regulation. EU regulation has recently started considering Combination Products as a separate group after the release of MDR 2017/745. That, too, EU MDR mentions only Drug Device Combination Products (DDCs).

The broad categorization of Combination Products remains the same across the jurisdictions. However, the definitions and terminologies used in different regulatory regions can vary. Combining a drug/biologic with a medical device has been shown to increase the efficiency and safety of the product[i] resulting in increased innovation and product registration. Per the EMA's annual report in 2019[iii], 25% of the approved medicines included a device component. However, there are legal, regulatory, and scientific concerns related to combining different medical products and technologies. These products require greater coordination and communication among stakeholders. Hence, regulations across the globe are also evolving continuously in response to the rapid growth in this field. These regulations can become complex as they differ significantly across jurisdictions.

The article focuses on Combination Products with a medical device as a constituent part and presents an overview of the current regulatory pathways for marketing approval in two different regulatory regions: The US and the EU. The article also discusses the post-marketing regulatory requirements and the current challenges that the manufacturers of this group of products may face in the changing regulatory landscape.

Background

The regulation in the EU, especially for Combination Products, is still in a nascent stage. However, in the US, the concept of these products was introduced almost half a century ago. The US Food and Drug Administration (FDA) developed regulations for Combination Products in the 1970s[iv]. These Combination Products included radio-biologics and in-vitro diagnostics. In 1990, the Safe Medical Devices Act (SMDA) was adopted, which designated the primary jurisdiction of the FDA for regulating Combination Products. The 21 CFR Part 3 was also introduced around the same time (in 1991). Eventually, SMDA fell under the FDA Modernization Act (FDAMA), which was enacted in 1997. However, some industry-perceived shortcomings in the FDAMA had the potential for disputes or disagreements[v] related to Combination Products.

Hence, the Office of Combination Products (OCP) was established[iv] in 2002 as required by Section 204 of the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) to address the unique challenges related to Combination Products. After two years of the birth of the OCP, the draft Current Good Manufacturing Practices (cGMP) for Combination Products was made available (in 2004) to guide the industry and FDA staff in achieving compliance with the applicable cGMPs for the biological product, device, or drug constituents of Combination Products as well as for the finished Combination Product. The draft cGMP was finalized in 2013 (codified in 21 CFR Part 4) after taking inputs and suggestions from stakeholders and experts. Section 3038 of the 21st Century Cures Act, enacted in December 2016, substantially amended section 503(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 USC 353(g)), the principal section of the FD&C Act addressing Combination Products.[iv]

Current status of the regulatory requirements

Though the regulation of Combination Products is comparatively new in the EU, the regulatory approach adopted is based on a more detailed classification of Combination Products compared to the US. Article 117 of the EU MDR 2017/745 has amended Directive 2001/83/EC governing medicinal products for human use and has introduced additional requirements for Combination Products.

Table 2: Comparison of the US and the EU approval processes for combination products

Approval Process	US	EU
Assessment of Combination Products	Application for a Combination Product is filed to an appropriate lead center which the OCP assigns for every Combination Product. The lead center could be any one of the three divisions of the FDA (CDER, CBER, and CDRH) based on which constituent part provides the primary mode of action (PMOA) of the Combination Product.	Application for a combination product is filed to EMA with either a Declaration of Conformity (OR) Certificate of Conformity (OR) Notified body Opinion that the device part complies with the relevant general safety and performance requirements of MDR. Based on the PMOA, the risk class of the product is assessed. Notified body involvement is required for assessing

Approval Process	US	EU
Assessment of Combination Products		the device part, except for Class I devices (non-measuring, non-reusable, non-sterile).
Marketing Approval	Irrespective of PMOA, each constituent part is assessed.	Each constituent part of a DDC goes through the approval process as applicable.
Regulatory Requirements for investigational application	• If PMOA is attributable to the drug/biologic, an Investigational new drug application (IND) is submitted. • If PMOA is attributable to the device, Investigational device exemption (IDE) is submitted.	• Suppose the action of the medicinal product (including a product derived from human blood or human plasma) is ancillary to that of the device. In that case, the PMOA is attributable to the device, and the Combination Product is assessed as a Class III device. • If the action of the medicinal product is principal, the integral Combination Product is governed by Directive 2001/83/EC or Regulation (EC) No 726/2004. The device part goes through conformity assessment as per MDR 2017/745.

Approval Process	US	EU
Requirement for submission of regulatory applications for marketing approval	• If PMOA is attributable to the drug, submission to CDER o New drug application (NDA) or o Abbreviated new drug application (ANDA) • If PMOA is attributable to biologic, submission to CBER o Biologic license application (BLA) • If PMOA is attributable to a device, submission to CDRH o Premarket Approval (PMA) application o De Novo designation o Pre-market notification (510 (k))	• Information on the safety and effectiveness of each component of the Combination Product. • If PMOA is attributable to the drug, o Marketing Authorization Application (MAA) for the drug constituent with structured information on the device constituent in eCTD format: This should cover all aspects related to the safety and performance of the product. This includes the manufacturing process, applicable controls, and usability data o Depending on the risk class of the medical device constituent, a Declaration of Conformity by the manufacturer or a relevant certificate by a notified body or notified body opinion is required. • If PMOA is attributable to the device, then the assessment is as per MDR 2017/745.
Information Center	OCP develops guidance/regulations for the applicants.	EMA develops guidance documents to guide applicants in providing consistent and complete information in a submission.

Approval Process	US	EU
Guidance Documents for Applicants	All guidance documents for Combination Products are publicly available on FDA's website and can be downloaded from https://www.fda.gov/combination-products/guidance-regulatory-information/combination-products-guidance-documents	Publicly available guidance documents can be downloaded from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-documentation-medicinal-products-when-used-medical-device-first-version_en.pdf. and Guidance - MDCG endorsed documents and other guidance (europa.eu)

The regulatory pathway to marketing authorization of a Combination Product is more difficult in the EU compared to the US, as a single marketing approval application is usually sufficient for a Combination Product in the US.

Regulatory pathway in the US

OCP Centers for Combination Product Review and Reporting

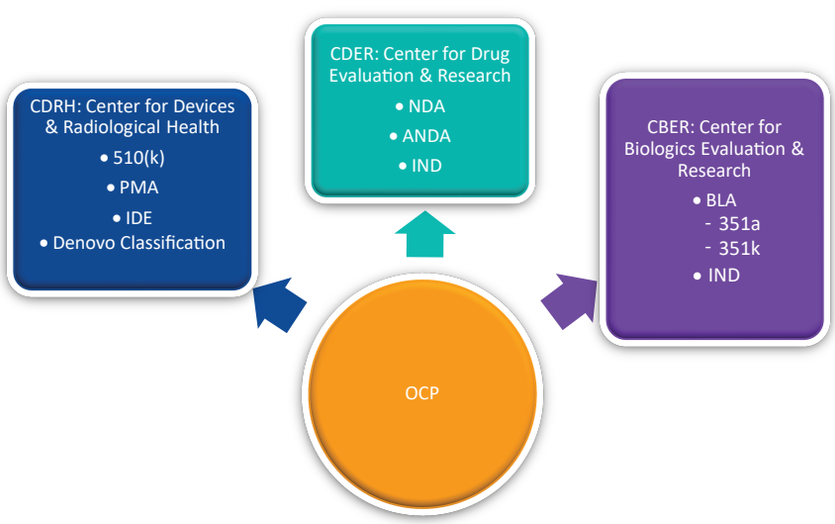

Figure 2: Lead Centers of Office of Combination Products

The OCP works as a facilitator or a primary focal point for the FDA agencies, consumers, and the industry in the US. The OCP usually assigns one lead center (CDRH, CDER, or CBER) based on the PMOA of the Combination Product rather than multiple centers to help avoid unnecessary duplications and streamline the review and reporting process. As per 21 CFR Part 3, PMOA is the single mode of action of the Combination Product that provides its most important therapeutic action[vi]. So, in the US, if the PMOA of a

drug/device Combination Product is attributable to the device, the lead center responsible for pre-market review would be the Center for Device and Radiological Health (CDRH). If the review of a Combination Product needs the involvement of more than one FDA center, the OCP uses an algorithm for center assignment. This is based on the expertise of a center in evaluating the safety and effectiveness of a similar type of Combination Product.

The OCP does not review the marketing applications, but it can be requested to be part of the regulatory meetings with the reviewers[vii]. It also plays an important part in resolving disputes related to the timeliness of pre-market review and pre-market review decisions on a Combination Product.[vii] In addition, OCP ensures patients' safety by setting guidelines and providing training (to industry and FDA staff) on the consistency and appropriateness of post-market activities required for such products.[viii] One can reach the OCP through the mail, email, or fax[vii] to submit a request for designation (RFD), as per the defined process in 21 CFR Part 3, to obtain a binding classification or lead center assignment[ix]. A lead center is assigned within 60 days of RFD filing. In 2011, FDA released a guidance document for the industry regarding the type of information the manufacturers should submit to help OCP determine the regulatory identity or classification of a product and, if applicable, assign the appropriate lead agency for review and regulation. The RFD should be submitted before filing any investigational or marketing applications to the FDA.

Alternatively, a manufacturer may submit a pre-RFD to obtain preliminary, informal, and non-binding feedback on the classification and to address jurisdictional issues. The sponsors are free to propose the classification and assignment they believe should apply to their product for a pre-RFD and are required to do so for an RFD. However, the OCP makes the final decision with input from the relevant divisions of the FDA. However, submitting RFD/pre-RFD is not mandatory if the manufacturer is clear about the classification of the product.

Regulatory pathway in the EU

In the EU, each constituent part of the DDC (integral with the medicinal product as PMOA or co-packaged or referenced) must go through the approval process. However, if the medicinal product has ancillary action, the Combination Product will be assessed and authorized as per MDR 2017/745. The level of regulatory scrutiny will depend on the risk associated with the product, which will depend on the product's intended purpose. In addition, the assessment of these products also considers the quality aspects of a

device and the use of the device with the medicinal product, including the impact of the device on the medicinal product. For example, if a medical device is intended to administer a specific medicine, it must be ensured that the device component doesn't adversely impact the characteristics of the medicine. Under the general rule, an application for marketing approval for an integral Combination Product must contain sufficient evidence demonstrating that the medical device constituent of the product complies with the relevant general safety and performance requirements (GSPRs) of MDR 2017/745. Notified body involvement may or may not be required depending on the class of the medical device. Moreover, for a non-integral Combination Product, the device constituent must carry a CE mark. The information contained in the submission concerning the manufacturing process, applicable controls, and usability should be sufficient for the regulating authority to assess the safety and performance-related factors. For instance, the applicant should provide detailed information about the platform used and justification for its users based on the product's intended purpose.[i]

In the EU, the devices are also required to indicate clearly on the label that they incorporate medicinal substances, human blood, or plasma derivatives. As there are no harmonized ISO standards for the Combination Product-related symbols, the European trade association has released a guide of symbols to comply with this requirement.[xiii]

The EU legal framework for Combination Products is based majorly on Directive 2001/83/EC (for medicinal products for human use), Regulation 726/2004/EC (for authorization and supervision of medicinal products for human and vet use), and Regulation 2017/745 (for medical devices) which amends Directive 2001/83/EC. In summary, the approach for Combination Products adopted in the EU is based on a slightly more detailed classification of such products than the FDA approach.[i]

Safety reporting requirements for marketed products

For the post-marketing regulatory requirements, the EU has yet to come up with clarifications on the specific post-marketing regulations for Combination Products, while FDA has finalized a rule which was prepared in consultation with various stakeholders. The main objective of the rule was to provide consistency in the Post Market Surveillance Report (PMSR) requirements and to avoid unnecessary duplicate reporting. At the same time, the promotion and protection of public health remained the primary focus.[xiv]

The following are the highlights of the PMSR rule:

- Standard definitions such as Combination Product applicant, constituent part applicant, device application, biological product deviation report (BPDR), correction and removal report, product development protocol (PDP), etc., have been given by the FDA for a better understanding of the relevant terms for all such submission types.
- The rule clarifies the difference between Application Type - Based Reporting Requirements and Constituent Part-Based Reporting Requirements
- This rule also clarifies which PMSR requirements apply for which of the constituents of Combination Products. In addition, it clarifies that duplicate reporting for the same event is not required.
- The rule considers that a substantial number of small entities are involved in a Combination Product lifecycle and commits that compliance with the rule would not have a significant economic impact on the small entities.
- If two entities A and B are jointly manufacturing a Combination Product, then both A and B will be subjected to provisions of this rule; however, there are provisions to avoid duplicate reporting. For instance, the constituent part applicants need to share the information on death or serious injury within the reporting period specified for that type of event. One of them can submit the combined report to the FDA.
- In addition to application type-based reporting requirements, the Combination Product applicant is required to submit reports to the FDA following timelines associated with the report type. If a Combination Product Applicant markets the constituent parts of the Combination Product under separate applications, the Combination Product Applicant must comply with the PMSR requirements associated with each application type. [xvi]

Report Type	Specific requirement	Timeline for Reporting	Types of reportable events	Record-keeping requirements
Field alert report (FAR)	Required only when the drug is one of the constituents.	Within 3 working days	Required for any incident that causes the product or its labeling to be mistaken for, or applied to another product, or any incident concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed product or failure to meet specifications	At least 10 years as per the requirements for medicinal products or at least 2 years beyond the expected life of the device (whichever is longer). Example: If a device constituent has an expected life of 10 years, the requirement for record keeping will be 12 years.
Fifteen-day report and *Follow-up report	Required irrespective of the type of constituents	15 calendar days if PMOA is biologic or drug, 30 calendar days if PMOA is a device	Required for serious and unexpected events	
Biological product deviation reporting (BPDR)	Required only when biologic is one of the constituents	Within 45 calendar days	Required for a deviation from a cGMP, applicable regulations, applicable standards, established specifications, or	

Report Type	Specific requirement	Timeline for Reporting	Types of reportable events	Record-keeping requirements
			an unforeseeable or unexpected event that may affect the purity, safety, or potency of the biologic constituent	
-Five-Day report and *follow-up report	Required only when the device is one of the constituents	No later than 5 working days.	Required for a reportable event that necessitates remedial action to prevent an unreasonable risk of substantial harm to public health or on the DA's request.	
-Malfunction report and *follow-up report		Within 30 calendar days.	Required for a product, or a similar product marketed by the applicant, malfunction that would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.	
-Correction or removal reports		Within 10 working days of initiating a correction or removal.	Required to reduce the risk to health posed by the product or remedy a violation of the FD&C Act caused by the product which may present a health risk.	

* Follow Up" reports for Fifteen-day, Five-day, and Malfunction reports are required when the Combination Product Applicants become aware of reportable new information related to the event that was not available at the time of the initial report.

Note: Some of the reporting requirements mentioned in the table may not apply if the event occurs outside the US. For foreign events, applicants should contact the Lead Center or OCP as needed.

Current challenges

An applicant for a Combination Product needs to know how the product will be reviewed and approved for sale and the mandatory post-market regulatory requirements. Drug manufacturers may feel challenged in complying with regulatory requirements related to the device constituent.

Marketing authorization challenges in the US

It may not be possible to determine PMOA for some Combination Products as the two constituents may have independent modes of action. Currently, OCP coordinates with two different lead centers in such cases. However, this may cause confusion regarding the regulatory requirements for the specific Combination Product. When more than one center is involved in the review process, the effectiveness of cooperation among the involved parties plays a critical role in determining the effectiveness of the review. In such cases, guidance from regulatory authorities/experts may be solicited for the type of marketing application requirement. Currently, separate marketing applications for individual constituents of a Combination Product are also permissible as per the FD&C Act, 503(g)(6).

For investigational Combination Products, typically, an Investigational New Drug (IND) application is submitted if the Combination Product has a drug or biologic PMOA, and an Investigational Device Exemption (IDE) is submitted if the Combination Product has a device PMOA. However, if both the combination's constituents (drug/biologic and device) are on the market individually and the RFD has been submitted for the Combination Product, will IND or IDE still be required? An applicant may discuss such issues with the regulatory authority (OCP in the US) to get assistance in understanding the regulatory nature of the Combination Product to determine the right pathway for marketing authorization.

Marketing authorization challenges in the EU

In the EU, all the constituents of the DDC product need to go through the approval process as per MDR 2017/745. Hence, a Combination Product needs to undergo two types of assessments: One independent assessment of the medical device as well as the drug and the other to assess the device's impact on the drug's safety and efficacy. In addition, no medical device can be grandfathered in the EU. Even if the Combination Product is on the market for a long time, the economic operators must ensure that it conforms to the current regulation. It indicates that any change in the packaging of medical products may lead to new regulatory requirements. For instance, if the packaging of a drug is changed in a way that it is marketed as a single entity with a dispenser, then the product may fall under the Combination Product category. Also, where a device part is replaced, or a new device is added, a new EU declaration of conformity/EU certificate may be required as part of a variation or extension application.

Article 117 of MDR 2017/745 adds a new requirement of the notified body opinion for the device part of an Integral drug-device Combination Product. The new requirement will apply according to the product's risk classification. An EU certificate issued by Notified Body for a device part must be provided in MAA. A manufacturer should seek a notified body opinion if the EU certificate is unavailable. Then a notified body opinion report will be issued, and it must be submitted during MAA. For Class I (non-sterile, non-measuring, and non-reusable) devices, the applicant should provide a Declaration of Conformity while submitting the MAA (NB opinion is not required).

Risk classification Requirement According to Article 117

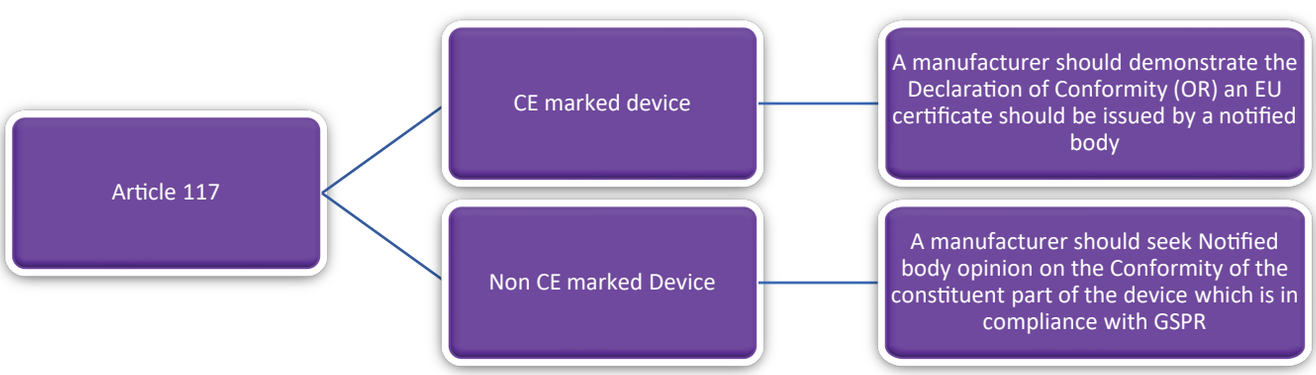

Figure 3: EU MDR Requirement: Article 117

As per Rule 14 of the MDR, incorporating a medicinal substance (including human blood or plasma derivative) into a device, where the action of the medicinal substance is ancillary to the device, puts it at the highest risk. Hence, all such medical devices are considered Class III medical devices, irrespective of their invasiveness or duration of use. These Combination Products must fulfill more comprehensive conformity assessment requirements for marketing authorizations.

Suppose the Combination Product is categorized as Class III under Rule 14 and the device part is implantable, or the device part is Class IIb; in this case, it needs to undergo extra scrutiny of the clinical evaluation consultation procedure by the independent expert panel. In addition, all the devices incorporating a medicinal product need to seek a scientific opinion from the medicinal product authority. No justification can replace the scientific opinion as per MDR 2017/745. The possible implication could be that despite complying with all stringent conformity assessment requirements for devices, the Combination Product may not get a certificate from the notified body if the scientific opinion is unfavorable.

Suppose the PMOA is a drug for a drug-device combination, and the device constituent falls under high-risk device due to its invasiveness or implantable nature; in this case, the product will take the marketing route as a drug complying with the Medicinal Product Directive (MPD). Still, the device part must also comply with appropriate conformity assessments required for a high-risk device.

In this evolving phase, when regulations for devices have become stricter, and the number of notified bodies has not increased proportionately, there is a significant amount of confusion related to the Combination Products. Getting a Combination Product on the market has become prolonged and more burdensome. The notified bodies are under tremendous time pressure for quality review. As drug manufacturers are also supposed to go through the device approval process for their Combination Products, the burden on the already burdened notified bodies will increase multifold. EMA released Guidelines on Combination Products (refer to Table 2) to help the applicants.

The applicant may contact the authorities responsible for medical devices to get additional clarifications on the product's regulatory status because general principles may not apply to all the products. The Combination Products are complex; hence, safety and effectiveness need to be assessed on a case-to-case basis. The manufacturers should engage in early dialogue with the concerned regulators.

It is important to understand what cannot be included as a Combination Product to avoid further confusion regarding the categorization and classification of products.

What is not a combination product?

Certain medical products are used in combination with each other. Hence, they may be mistaken for combination products. For example, syringes are primarily used to deliver a drug. However, unless it is specified on the label that the syringe can be used only with a specific drug, the syringe and the drug are not considered a Combination Product.

Suppose a medical product is used with a non-medical product; it doesn't fall under the Combination Product category - for example, a drug with a food supplement or a device with cosmetics. Moreover, suppose the same medical products (drug/drug or device/device) are used together; they do not fall under the Combination Product category, such as fixed-dose drug combinations.

In addition, each regulatory jurisdiction has its definition of a Combination Product. For example, a drug and biologic combination is not considered a Combination Product in the EU region.

Conclusion

Combination Products' regulations have been introduced to overcome the challenges in inventing, developing, manufacturing, and approval processes. Because of the increased safety and convenient use of Combination Products, the demand for such products is increasing. However, the Combination Products are complex and may deploy new methods and innovative technologies. The regulatory assessment of such products aims to ensure users' safety while supporting innovation. As the number of different types of Combination Products is increasing, the regulation for such products is also evolving.

Moreover, different countries have different regulations and definitions that add to the already existing challenges for the manufacturers. Hence, Combination Product manufacturers must understand and comply with the relevant regulatory requirements and remain vigilant about regulatory changes that could impact their product. A good understanding of the safety and efficacy profile of a Combination Product, as well as relevant regulations, will lead to the successful marketing of the product and technical success for patient treatment.

Preparing for Combination Product Registrations

A multidisciplinary team with varied and extensive knowledge regarding regulations and nuances in different markets is a necessity for a successful application. Regulatory strategists with experience making submissions FDA and EMEA, must work collaboratively with skilled and knowledgeable medical writers, toxicologists, and clinical teams to submit high-quality submissions to health authorities. A robust quality management system is necessary to ensure all checkpoints are reviewed for consistency and accuracy within the time permitted by the regulatory calendar.

References:

i. Guideline on quality documentation for medicinal products when used with a medical device. EMA/CHMP/QWP/BWP/259165/2019
ii. https://www.fda.gov/combination-products.
iii. The combination of medical devices and medicinal products revisited from the new European legal framework
iv. D.C. Schillinger. The office of combination products: its roots, its creation, and its role. https://dash.harvard.edu/handle/1/8852096 (2004)
v. Committee on Energy and Commerce. 2001. Evaluating the Effectiveness of the Food and Drug Administration Modernization Act. GPO.gov. http://www.gpo.gov/fdsys/pkg/CHRG-107hhrg72831/html/CHRG-107hhrg72831.htm
vi. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A part-3/subpart-A/section-3.2
vii. https://www.fda.gov/media/106799/download
viii. https://www.fda.gov/about-fda/office-clinical-policy-and-programs/office-combination-products
ix. https://www.fda.gov/combination-products/rfd-process
x. https://www.fda.gov/media/80495/download
xi. https://www.fda.gov/media/102706/download
xii. https://www.fda.gov/media/119958/download
xiii. MedTech Europe, 2019. Use of symbols to indicate compliance with the MDR - Version 2.0 (December 2019), Resource Library. European Union, pp. 1–16. https://www.medtecheurope.org/wp-content/uploads/2019/05/191217_MD-labelling_Symbols-guidance_REVISED_ FINAL.pdf
xiv. https://www.federalregister.gov/documents/2016/12/20/2016-30485/postmarketing-safety reporting-for-combination-products
xv. Postmarketing Safety Reporting for Combination Products. A Rule by the Food and Drug Administration on 12/20/2016
xvi. https://www.fda.gov/media/111788/download
xvii. Questions & Answers for applicants, marketing authorisation holders of medicinal products and notified bodies with respect to the implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)
xviii. MDCG 2020-12. Medical Device Coordination Group, 2020. Guidance on transitional provisions for consultations of authorities on devices incorporating a substance which may be considered a medicinal product and which has action ancillary to that of the device, as well as on devices manufactured using TSE susceptible animal tissues (June 2020), MDCG 2020-12. European Union, pp. 1–6. https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2020 12_guidance_transitional_provisions_en.pdf.

About ClinChoice

ClinChoice is a leading global Contract Research Organization (CRO), with over 4000 clinical research, regulatory, product vigilance, and toxicology professionals across North America, Asia, and Europe. For more than 28 years, ClinChoice has been providing high-quality contract research services to pharmaceutical, biotechnology, medical device, vaccine, and consumer healthcare product clients, encompassing a broad range of services and therapeutic areas.