COMBINATION PRODUCTS
GLOBAL REGULATORY LANDSCAPE

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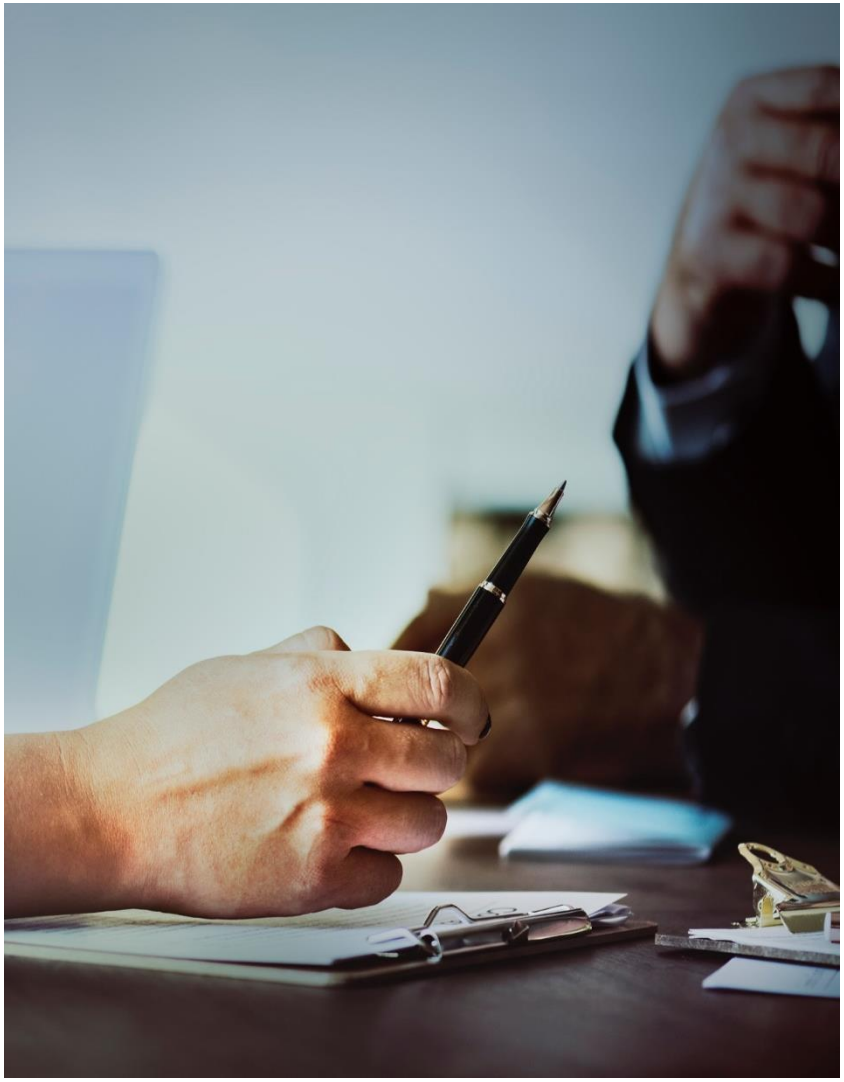
AGENDA



Introduction

Agenda

Background Information

- General Concept - Definition
- Benefits
- Market Overview

Global Regulatory Overview

- US
- EU
- Others: Canada, Japan, Australia, Brazil, China, etc…

Conclusion - Summary

GENERAL CONCEPT - DEFINITION

- Combination products (CP) are usually considered to be products which consist of **two or more regulated products** such as drug-medical device, biologic-medical device, drug-biologic, vaccine-medical device, or drug-medical device-biologic
- It is its **own product category**
- **Different regulatory controls** in comparison to the traditional requirements enforced on Medical Device, Drug, and Biologics

BENEFITS – GENERAL ADVANTAGES

Contribution to advancing medical care

Reduction of occurrence and intensity of adverse side effects

Improvement patient compliance

Drug release / administration control

Reduction of infection rates

Minimally invasive techniques support

Facilitate early diagnosis and reduced treatment duration

Pain minimization

Heightened cost efficiency

- Rapid recovery - reduced hospital stay
- Home-care

Improvement of safety, efficacy and/or effectiveness

MARKET OVERVIEW

These benefits have **boosted the demand** for these systems → **growth opportunities.**

More and more manufacturers of pharmaceuticals or medical devices are developing and incorporating **new technologies** to their core products.

- Impact: Pharmaceutical and MedTech marketplace being shaken up.

Approximately 30% of all new healthcare products currently under development are combination products

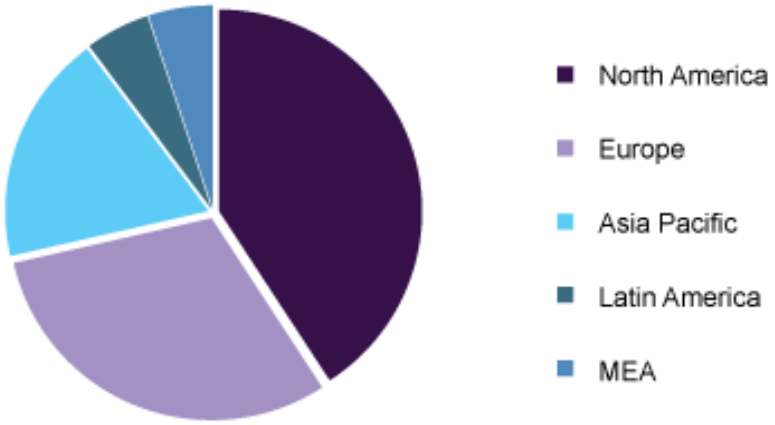
Global combination products market **in 2017 was reported as $30.5 billion USD** and it's predicted to reach an estimated value of **$115 billion USD by 2019**, with many predicting it will achieve **$178 billion USD by 2024.**

MARKET OVERVIEW

North America dominates the global combination products market in terms of revenue.

Asia-Pacific is considered the **most lucrative** growth market.

Global drug-device combination product market share, by region, 2015 (%)

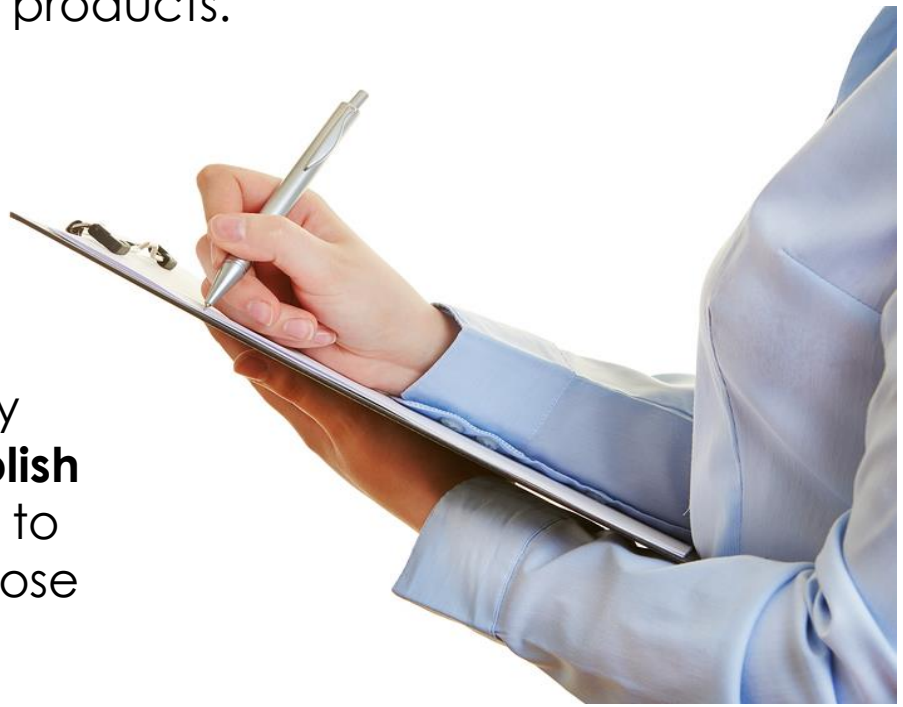


Drug Device Combination Products Market Size, Share & Trends Analysis Report By Product (Transdermal Patches, Infusion Pumps, Inhalers, Drug Eluting Stents, Antimicrobial Catheters), And Segment Forecasts, 2018 - 2024

WE NEED AN APPROPRIATE REGULATORY FRAMEWORK!

With the rapid evolution of combination products, the established regulatory frameworks which are intended to control defined product categories (i.e. medical devices, medicinal products/drugs, biological products, etc…) were **not suitable to ensure adequate controls** for these products.

With the increased prevalence of Combination Products and the obvious growth opportunities, many regions have felt the need to **establish appropriate regulatory frameworks** to control these products for the purpose of assuring public health.



US - CP REGULATORY FRAMEWORK

DEFINITIONS:

Combination Product: A product composed of any combination of a drug and a device; Under 21 CFR 3.2 (e).

- Device - Drug / Device – Biologic / Drug - Biologic / Device - Drug – Biologic
- **Types:** (21 CFR 3.2 (e)) Single entity / Co-packaged / Cross-labeled
- *Note: Combinations of a medical product with a non-medical product, for example a drug with a dietary supplement, cosmetic, or food, are not combination products.*
- **Constituent Parts:** Drug, device and biologic products in the combination products are referred to as "constituent parts".

Component: (21 CFR 820.3 and 210.3) ingredients, raw material, plastic components, sub-assemblies.

Primary Mode of Action (PMAO): Section 503(g) defines primary mode of action as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product" (see also definitions at 21 CFR 3.2.

US - CP REGULATORY FRAMEWORK

EXAMPLES:

Single Entity:

- Drug-eluting stent, pacing lead with steroid-coated tip, catheter with antimicrobial coating, condom with spermicide, transdermal patch
- Prefilled drug delivery systems (syringes, insulin injector pen, metered dose inhaler)

Co-packaged combination products (the components are packaged together) (21 CFR 3.2(e)(2)):

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

Cross-labeled combination products (components are separately provided but specifically labeled for use together) (21 CFR 3.2(e)(3) or (e)(4)):

- Photosensitizing drug and activating laser/light source

US - CP REGULATORY FRAMEWORK

OFFICE OF COMBINATION PRODUCTS (established on December 24, 2002)

- Sec. 204 of the Medical Device User Fee and Modernization Act of 2002 (MDUFMA).
- Sec. 503(g) of the Federal Food, Drug, and Cosmetic Act (21 USC 353(g)

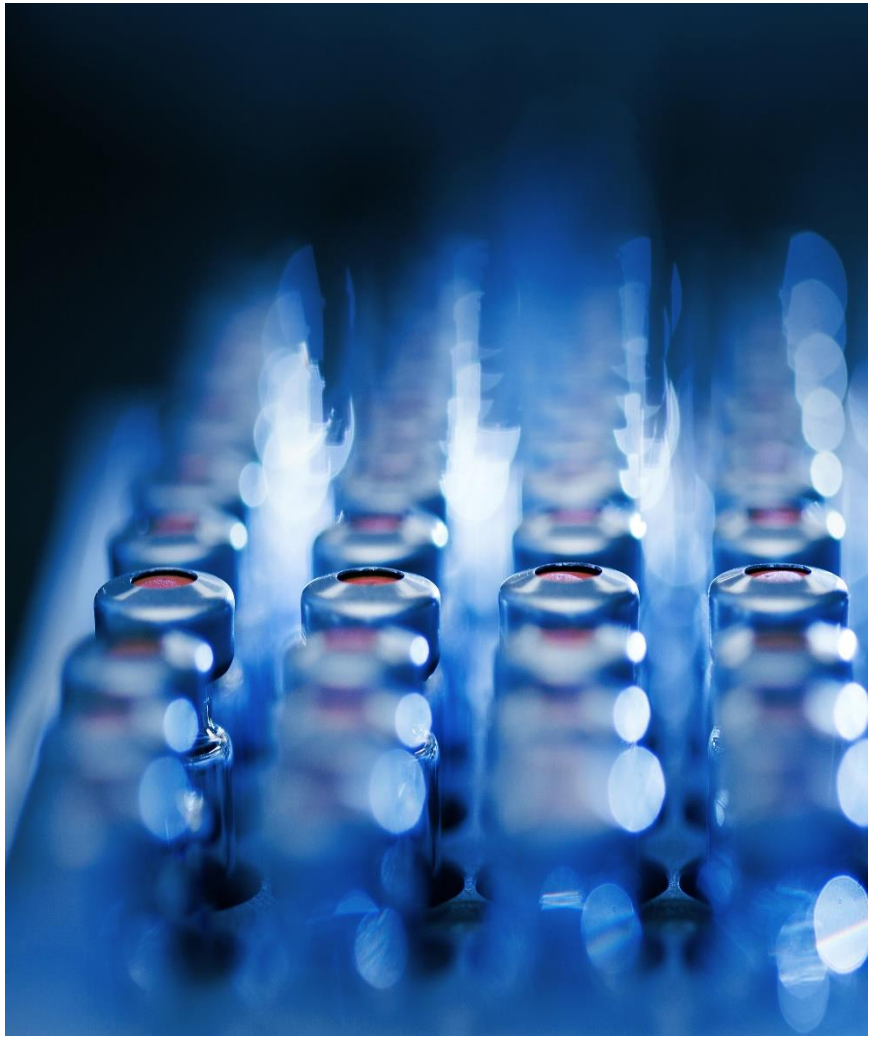
ROLES:

- **Focal point** for combination product issues, for medical product classification and assignment issues for agency staff / industry.
- Develop **guidance** / regulations to clarify the regulation of combination products.
- **Classify** medical products as drugs, devices, biological or combination products and assign them to an FDA center for premarket review and regulation, where their classification or assignment is unclear or in dispute.
- Ensure timely / effective premarket review of combination products by overseeing the timeliness, **alignment of coordination** of reviews involving more than one agency center, including through monitoring and management of the intercenter consult process
- **Ensure consistent** / appropriate postmarket regulation of combination products.
- **Resolve disputes** regarding the timeliness of premarket review of combination products.

US - CP REGULATORY FRAMEWORK

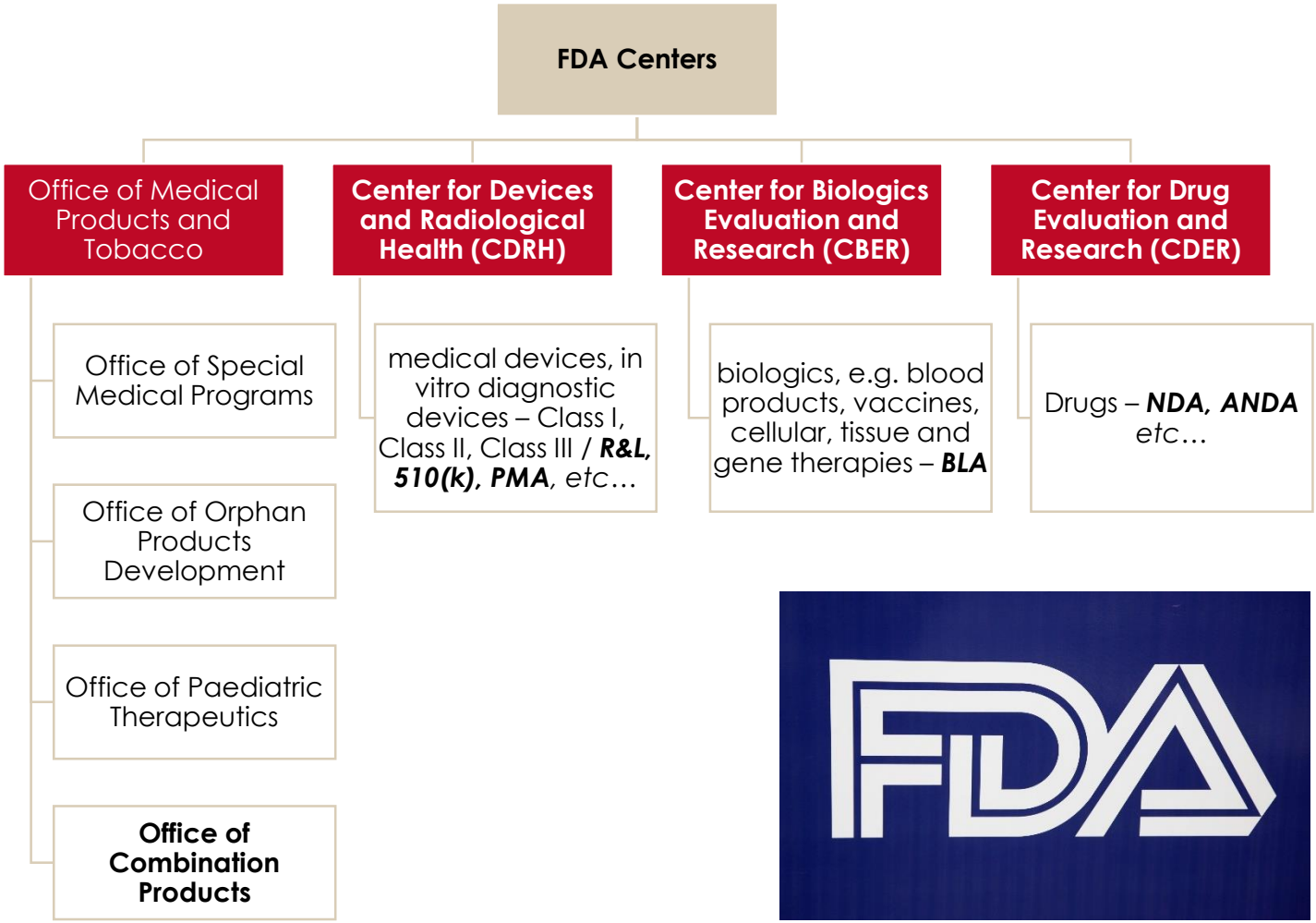
REQUEST FOR DESIGNATION (RFD)

- PMOA is unclear,
- Sponsor can petition the OCP to assign its product to a review center through a Request for Designation (RFD), also known as letter of request.
    - Recent introduction of Pre-RFD. (non-binding)
- Sponsor can suggest how a product should be categorized.
- 60 days to agree or disagree with the sponsor's proposed classification.
- Once the OCP decision is final, and the designated center will regulate all decision-making regarding the approval and risk classification of the product.



US - CP REGULATORY FRAMEWORK

FDA CENTERS/APPROVAL PATHWAY:



US - CP REGULATORY FRAMEWORK

CGMP REGULATIONS:

Final rule: 21 CFR Part 4

- cGMP Requirements for Combination Products (effective July 22, 2013)
- Draft guidance (January 2015)
- Final guidance (January 2017)

Notes:

- Part 4 does not introduce new requirements but aligns the existing requirement (21 CFR 210/211, 820).
- Investigators with expertise in pharmaceuticals and medical devices are sent to combination product manufacturers.

US - CP REGULATORY FRAMEWORK

21 CFR Part 4 cGMP Requirements: "Streamlined Approach" Concept

Type	Device Only	Drug Only	Combination Product
Examples	Manufactures only the auto injector	Manufactures only the epinephrine	Final Assembly/Final product owner/Sponsor
Regulations	QSR - 21 CFR 820	cGMP - 21 CFR 210/211	21 CFR Part 4
	MDR – 21 CFR 803	AER – 21 CFR 314	PMSR - Combination

Similarities:

- Focus on management, organization, and personnel
- Documentation and record keeping requirements
- Flexible in some aspects and prescriptive in others
- Objective is to ensure control and assure the quality of the manufactured products

US - CP REGULATORY FRAMEWORK

STATUTORY PROVISIONS

- 21st Century Cures Act, Section 3038. Combination Product Innovation, December 13, 2016
- 21 USC 360bbb-2 - Statutory provisions pertaining to classification and assignment of medical products can be found in section 563 of the Federal Food, Drug, and Cosmetic Act
- 21 USC 353(g) - Statutory provisions relating to the assignment of combination products to Agency components, to their premarket and postmarket regulation, and to associated responsibilities of Agency components including the Office of Combination Products can be found at section 503(g) of the Federal Food, Drug, and Cosmetic Act Statutory definitions
    - 42 U.S.C. 262(i) and 21 CFR 600.3(h) - Biological product – section 351(a) of the Public Health Service Act
    - 21 U.S.C. 321(g) - Drug - section 201(g) of the Federal Food, Drug, and Cosmetic Act
    - 21 U.S.C. 321(h) - Device - section 201(h) of the Federal Food, Drug, and Cosmetic Act
    - 21 U.S.C 353 (g) - Combination product - section 503(g) of the Federal Food, Drug, and Cosmetic Act

US - CP REGULATORY FRAMEWORK

REGULATIONS

- 21 CFR Part 4 – the regulations pertaining to current good manufacturing practices and postmarket safety reporting requirements for combination products
  - Final rule on postmarketing safety requirements for combination products, December 20, 2016
  - Final rule on current good manufacturing practice requirements for combination products, January 22, 2013
- 21 CFR Part 3 - the regulations pertaining to the classification of medical products as drugs, devices, biological products, or combination products and their assignment to FDA components for premarket review and regulation
  - 21 CFR 3.2(e) – Definition of a combination product
  - 21 CFR 3.7 – requirements for RFD submissions
  - Final rule to define "mode of action" (MOA) and "primary mode of action" (PMOA), August 25, 2005
- Proposed rule to amend regulations concerning the classification of products as biological products, devices, drugs, or combination products, and their assignment to Agency components for premarket review and regulation. May 15, 2018

EU - CP REGULATORY FRAMEWORK

DEFINITIONS:

Combination Product: Not defined.

- Products which align with the general combination products concept are regulated as either **medical devices or medicinal products**.
- The determination for which regulatory framework is applicable for a combination product is based on a **similar approach** to the US **PMOA.** However, the **criteria and method** for the determination **are different** with the possibility of resulting in a **different conclusion**.
- These products are referred to as "**drug-device combinations**".

Regulatory Context:

- In 2017, EU began the implementation phases of it **new regulatory framework** as it introduces the Medical Device Regulation (MDR – until May 2020), and the Invitro Diagnostics Regulations (IVDR – until May 2022).
- The new regulations **assign responsibilities to Notified Bodies (NB)** to review medical devices portions of device-drug combinations.

EU - CP REGULATORY FRAMEWORK

REGULATORY CHALLENGES:

- Drug / life science manufactures which are incorporating medical devices to their products will **now need to interact with NB**
- The number of **NB** have and will continue to diminish since the introduction of the new regulations, meanwhile the **level of responsibilities have increased** (i.e. combination products)
- Medicinal Products review the safety **of the drug** while the CE process controls separately **the device entity**. Therefore, gaps may exists as the overall quality, safety or efficacy of the medicinal product is not reviewed using a holistic approach, **unless it is considered "integral"**.

CANADA - CP REGULATORY FRAMEWORK

DEFINITIONS:

Combination Product: Is a therapeutic product that combines a drug component and a device component (which by themselves would be classified as a drug or a device), such that the distinctive nature of the drug component and device component is **integrated in a singular product**.

Immunological: Is understood as an action in or on the body by stimulation and/or mobilization of cells and/or products involved in a specific immune reaction.

Metabolic: Is understood as an action which involves an alteration of the normal chemical processes participating in, and available for, normal body function. The fact that a product is itself metabolized does not imply that it achieves its principal intended action by metabolic means.

Pharmacological: Is understood as an interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent and, for the purposes of this policy, includes anti-infective activity.

Therapeutic Products Classification Committee: Is a committee appointed by the Director General of TPD to develop, maintain, evaluate and recommend for approval policies, procedures and guidelines concerning the classification and review of therapeutic products as drugs, devices or combination products; to assess submissions for combination products referred to it and determine an appropriate classification and review mechanism for the submission.

CANADA - CP REGULATORY FRAMEWORK

APPLICABLE REGULATIONS:

- the Medical Devices Regulations
- the Food and Drug Regulations; or
- the Natural Health Products Regulations.

CLASSIFICATION PROCESS:

- Handled by the Health Products and Food Branch (HPFB).
- When unclear, the Office of Science of the Therapeutic Products Directorate is consulted.
- If necessary, the members of the Therapeutic Products Classification Committee (TPCC) are further consulted.
    - Methodology covered in guidance document: Classification of Products at the (Medical) Device-Drug Interface

CANADA - CP REGULATORY FRAMEWORK

APPLICATION APPROACH:

- The drug component of a combination product must comply with **the Food and Drug Regulations** and the device component must comply with the **Medical Devices Regulations.**
- **Principal mechanism of action** for the intended purpose similar to the PMOA approach.
- Sponsor can recommend jurisdiction with supporting information (30 day review)
- Policy effective 2006.

JAPAN - CP REGULATORY FRAMEWORK

DEFINITIONS:

Combination Product:

- Combination products are products consisting of two or more pharmaceutical drugs and medical devices. These products are expected to **fall under the category of drugs, medical devices, or cellular and tissue-based products if marketed individually**

Regulations:

- Revised Pharmaceutical Affairs Law, the following notifications have become effective:
    - **Handling of Marketing Application for Combination Products** (PFSB/ELD Notification No. 1024-2, PFSB/ELD/OMDE Notification No. 1024-1, PFSB/SD Notification No. 1024-9, PFSB/CND Notification No.1024-15).

Classification:

- Products **are individually judged** as to whether they fall under the category of drugs, medical devices, or cellular and tissue-based products by taking their primary function and purpose into consideration.

JAPAN - CP REGULATORY FRAMEWORK

Classification of combination products include:

- Set products which consist of individual drugs that can each be marketed individually as a drug, medical device, or cellular and tissue-based product;
- Kit products specified in PAB/ELD Notification No. 2-98; and
- Products in which the constituting drugs is unable to be marketed individually (excluding kit products).

Classification of combination products include:

- Additional classification of combination products includes:
- Products which contain medical devices for puncture and external disinfectants used as a drug for disinfecting the skin at the puncture site that are combined and packaged together and sterilized according to PFSB/ELD/OMDE Notification No. 0331002;
- Products which contain marketed drugs, medical devices, or cellular or tissue-based products that are sold together by distributors and are handled according to Handling of combination drugs etc. (PMSB/IGD Notification No. 104); and
- Drugs approved for integral marketing with devices specified in article 98-2 and article 228-20-3 of "Medical Devices Approved for Integral Marketing with Drugs", article 114-60-2 and Cellular and Tissue-based Products Approved for Integral Marketing with Devices etc.", and/or article 137-60 of Ordinance of the Ministry of Health and Welfare No.1 of 1961.

CHINA - CP REGULATORY FRAMEWORK

DEFINITIONS:

Combination Product:

- The drug-device combination product refers to a product that involves a medical device and a drug and produced **as a single entity.**

Regulations:

- The China Food and Drug Administration issued the "Guideline for Registration of Drug-Device Combination Product" in 2009

Classification of combination products include:

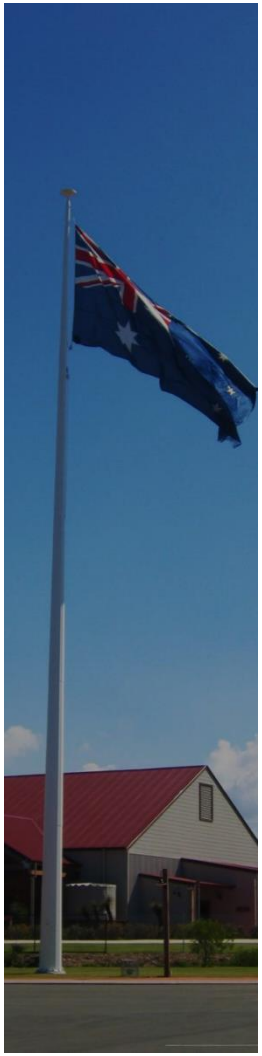
- For the drug-device combination products whose primary mode of action is drug, it should submit the **drug registration**. If the primary mode of action is medical device, it should submit the **medical device registration**.

CHINA - CP REGULATORY FRAMEWORK

Classification of combination products include:

- If a product has not been identified in China as a drug-device combination product, the applicant shall submit **a product classification request to CFDA** before submitting the registration application.
  - CFDA team of experts reviews the product classification request within 20 business days
- **First-time import drug-device combination product**, the application **will not be accepted if this product has not been approved by the home countries (regions)**. If the drugs involved in the combination products have not been registered or have not been approved by the producing country (region), the application will also not be accepted.

AUSTRALIA - CP REGULATORY FRAMEWORK



REGULATIONS:

Combination products are regulated as medicines under the TG Act.

If a combination product incorporates two or more product types, it is **strongly recommended to review device/ medicine boundary products information on the TGA website.**

BRAZIL - CP REGULATORY FRAMEWORK

REGULATIONS:

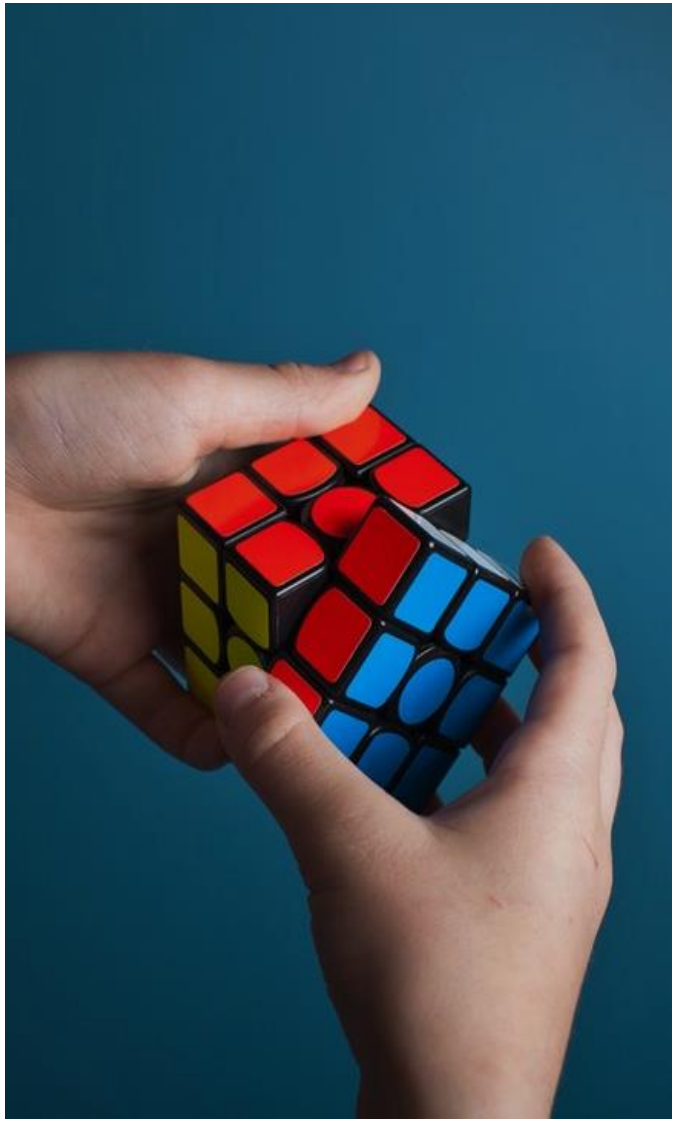
Combination products are **not subject to a specific regulation**.

To establish the pathway, a relevant aspect to be considered is whether the device would be **commercialized within the drug packaging or independently**.

- In the latter case, the device will need to comply with **Resolution No. 185 of 22 October 2001**, which establishes general conditions for **approval, marketing and review of medical devices**.

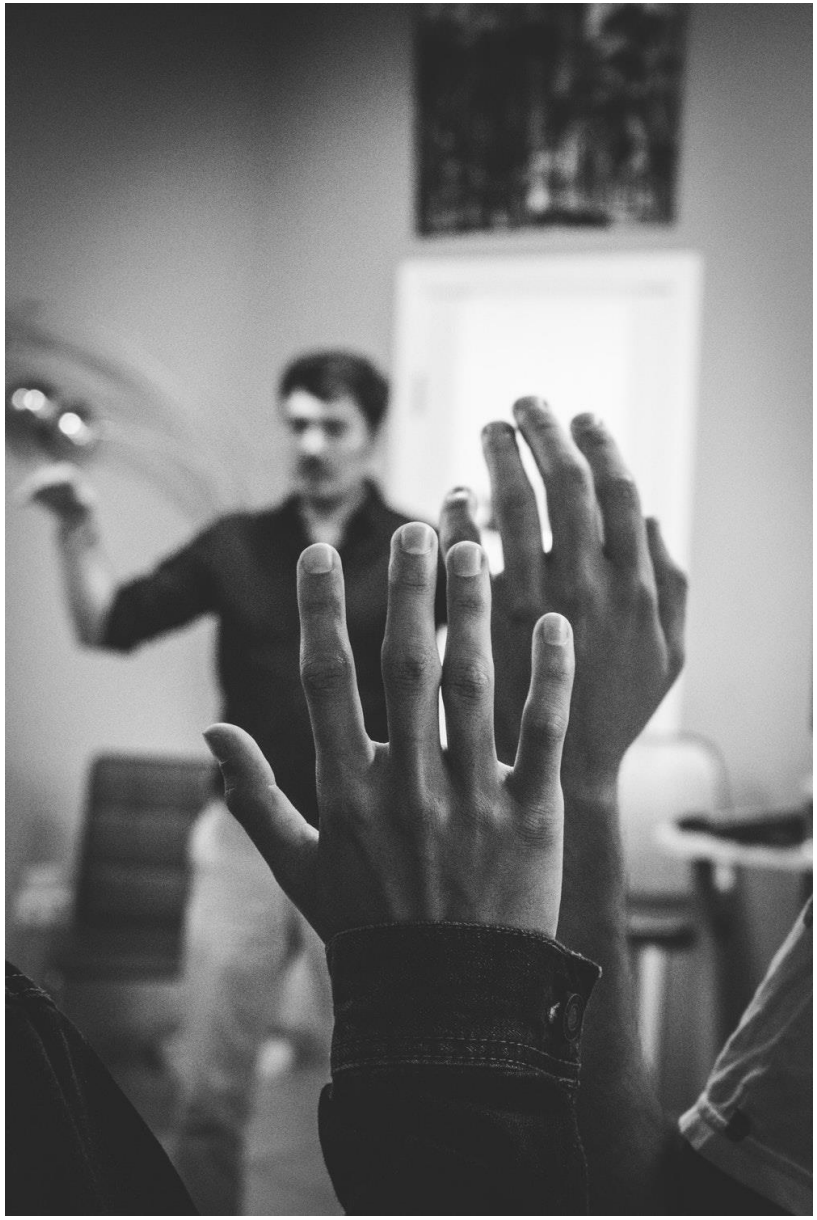
KEY POINTS

- Innovation is occurring in combination products.
- Major industry growth are anticipated for the upcoming years.
- Industry still at it infancy, therefore more regulations and guidelines can be expected.
- Combination Product definitions are not harmonized.
- The concept of primary mode of action appears to be adopted by many jurisdictions however the criteria for determination are not always aligned.
- The approval process is not always clear and often diverge from one jurisdiction to another.
- Early consultation with targeted jurisdiction is strongly recommended.
- Consider drug-device interaction evaluations during the development and the manufacturing of the product.



RECOMMENDATIONS

- Define the PMOA accurately to support your proposed classification for your regulatory strategy.
- Research the global regulatory guidelines and engage with the targeted competent authorities early on.
- Develop an appropriate cGMP quality compliance strategy taking in consideration relevant controls for devices and medicinal products.
- Align the drug development and device development processes within the organizations to ensure full coverage of device and drug requirements, while minimizing redundancies.
- Adopt risk based decision making methods
- Develop stability programs on the overall product and not just the device or drug components separately.



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