

REGULATIONS FOR COMBINATION PRODUCTS AND MEDICAL DEVICES

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- REGULATORY AFFAIRS

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- ▶ A **combination product** is a product 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.

Example: -

- ▶ Monoclonal antibody combined with a therapeutic drug
- ▶ Device coated or impregnated with a drug or biologic
- ▶ 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)

SOME EXAMPLES OF COMBINATION PRODUCTS:

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**ReoPro – Anticoagulant
Monoclonal Antibody(Single Entity CP)**



**Prefilled DDS(Syringes,
insulin injector pen, metered dose inhaler)**

MEDICAL DEVICES :

- ▶ A medical device is an instrument, apparatus, in vitro reagent , implant or other similar or related article, which is intended for use in the **diagnosis** of disease or other condition ,or in the **cure** , **mitigation** , **treatment** , or **prevention** of disease or intended to affect the structure or any function of the body and which does not achieve any of its primary intended purposes through its chemical action within or on the body.

In US, FDA has 3 assigned centers for regulation:

- ▶ 1. Center for Drug Evaluation and Research (CDER) (for **combination product**)
- ▶ 2. Center for Devices and Radiological Health (CDRH) (for **Devices**)
- ▶ 3. Center for Biologics Evaluation and Research (CBER)

Example: Wound dressing with antimicrobial — typically a device (CDRH)

- ▶ Asthma inhaler or medicinal patch — typical a drug (CDER)

What is a medical device?

Defined in s41BD of the *Therapeutic Goods Act 1989*

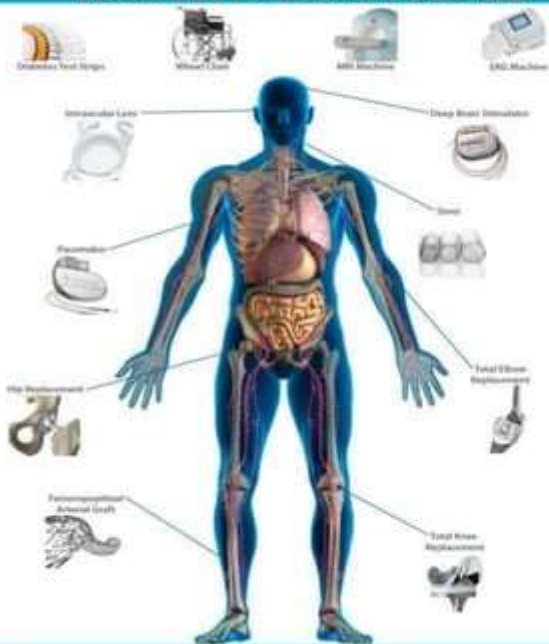
Any instrument apparatus, appliance, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended to be used for human beings for:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap;
- investigation, replacement or modification of the anatomy or of a physiological process;
- control of conception; or
- an accessory to an instrument, apparatus, appliance, material or other article mentioned above

It may not achieve its principal intended action by pharmacological, immunological or metabolic means, but may be assisted by such means



EXAMPLES OF MEDICAL DEVICES



Medical Devices



Type	Description	Common Example(s)
1	<p>Convenience Kit or Co-Package</p> <p><i>Drug and device are provided as individual constituent parts within the same package</i></p>	Drug or biological product vials packaged with device(s) or accessory kits (empty syringes, auto-injectors, transfer sets), first aid or surgical kits containing devices and drugs
2	<p>Prefilled Drug Delivery Device/ System</p> <p><i>Drug is filled into or otherwise combined with the device AND the sole purpose of the device is to deliver drug</i></p>	Prefilled drug syringe, auto-injectors, metered-dose inhalers, dry powder inhalers, nasal-spray, pumps, transdermal systems, prefilled iontophoresis system or microneedle "patch"
3	<p>Prefilled Biologic Delivery Device/ System</p> <p><i>Biological product is filled into or otherwise combined with the device AND the sole purpose of the device is to deliver biological product</i></p>	Vaccine or other biological product in a prefilled syringe, autoinjector, nasal spray, transdermal systems or microneedle patch pre-loaded with biological product
4	<p>Device Coated/ Impregnated/ Otherwise Combined with Drug</p>	Drug pills embedded with sensors, contact lens coated with a drug, drug-eluting stents, drug-eluting leads, condoms with spermicide, dental floss with fluoride, antimicrobial coated catheters/sutures, bone cements with antibiotics

5	<p>Device Coated or Otherwise Combined with Biologic</p> <p><i>Device has an additional function in addition to delivering the drug</i></p>	<p>Live cells seeded on or in a device scaffold, extracorporeal column with column-bound protein</p>
6	<p>Drug/Biologic Combination</p>	<p>Antibody-drug conjugates, progenitor cells combined with a drug to promote homing</p>
7	<p>Separate Products Requiring Cross Labeling</p>	<p>Light-activated drugs or biological products not co-packaged but labeled for use with a specific light source device</p>
8	<p>Possible Combination Based on Cross Labeling of Separate Products</p>	<p>Drug/biological product under development utilizes a device, but unclear whether the final product will require that the two be cross-labeled</p>
9	<p>Other Type of Part 3 Combination Product (e.g., Drug/Device/ Biological Product)</p> <p><i>Combination product not otherwise described</i></p>	<p>All 3 articles are combined in a single product (e.g., a prefilled syringe containing an antibody-drug conjugate), device to manufacture a biologic also includes a drug or biologic in the kit, or the product contains two different combination product types (e.g., Type 1 and Type 2 are provided together</p>

ARTICLES DECLARED NOT TO BE MEDICAL DEVICES :

Therapeutic Goods (Articles that are not Medical Devices) Order No. 1 of 2010 declares that the following ~~are not~~ medical devices:

1. Chemical oxygen generators
2. In-vivo imaging agents
3. Product intended to deliver a medicine, where the medicine and device are a **single integral product** (which is not reusable)
4. Products incorporating tissues, cells, substances of **human origin**
5. Products incorporating **viable** tissues, cells, substances of animal origin
6. Hospital and household grade disinfectants

SOFTWARE – IS IT A MEDICAL DEVICE?

A software product is a medical device if it meets the definition of a medical device (s41BD of the Therapeutic Goods Act 1989).

Examples

- Mobile app used to measure blood glucose levels for monitoring diabetes.
- Software which analyses and interprets ECG signals.
- Software running an infusion pump to control dose delivery.

Who regulates medical devices?

Australia	• Therapeutic Goods Administration (TGA)
Europe	• Certification is obtained from a Notified Body
USA	• Food and Drug Administration (FDA)
Canada	• Health Canada
China	• The State Food and Drug Administration (SFDA)
Japan	• Ministry of Health Labour and Welfare (MHLW)
Brazil	• ANVISA

Determine your target markets

OFFICE OF COMBINATION PRODUCTS (OCP) :

- ▶ The Office of Combination Products was established on **December 24, 2002** as required by Sec. 204 of the Medical Device User Fee and Modernization Act of 2002 (MDUFMA).
- ▶ Its duties are detailed in section 503(g) of the Federal Food, Drug, and Cosmetic Act ([21 USC 353\(g\)](#))

THE ROLES OF THE OFFICE OF COMBINATION PRODUCTS (OCP) INCLUDE:

- ▶ To serve as a focal point for combination product issues and for medical product classification and assignment issues for agency staff and industry.
- ▶ To develop guidance and regulations to clarify the regulation of combination products.

- ▶ To classify medical products as drugs, devices, biological products 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.
- ▶ To ensure timely and 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.
- ▶ To ensure consistent and appropriate postmarket regulation of combination products.
- ▶ To resolve disputes regarding the timeliness of premarket review of combination products.

Office of Combination Products staff members:

- ▶ **Thinh X. Nguyen - Director**
- ▶ **Patricia Y. Love, MD., MBA. - Deputy Director**
- ▶ **John (Barr) Weiner, J.D. - Associate Director for Policy and Product Classification Officer**
- ▶ **Leigh Hayes, J.D. – Lead Product Jurisdiction Officer**
- ▶ **Joseph Milone, Ph.D. - Senior Scientific Reviewer**
- ▶ **Jose L. Moreno, Ph.D. - Senior Scientific Reviewer**
- ▶ **Diana M. Yoon, Ph.D. - Senior Scientific Reviewer**
- ▶ **Melissa Burns - Senior Program Manager**
- ▶ **Bindi Nikhar, MD. - Associate Clinical Director**
- ▶ **Maryam Mokhtarzadeh, MD. – Senior Medical Officer**
- ▶ **Bibi K. Jakrali - Management Analyst**
- ▶ **Danita M. Dixon - Project Management Officer**

HOW ARE COMBINATION PRODUCTS ASSIGNED FOR REVIEW?

Combination products are assigned to a **FDA center** that will have **primary jurisdiction** for its premarket review and regulation.



Determination of the “**primary mode of action**” (PMOA) of the combination product. (provides the most important therapeutic action of the combination product)



In some cases, the **most important therapeutic action cannot be determined**. For example, a combination product may have **two independent modes of action**, neither of which is subordinate to the other.



FDA's regulations at [21 CFR Part 3](#) include an **algorithm** for determining center assignment.

- ▶ **FDA's Center for Devices and Radiological Health (CDRH)** is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in **the United States**.
- ▶ FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels.
- ▶ Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device.
 - ▶ 1. Class I devices are exempt from Premarket Notification (**lowest risk**)
 - ▶ 2. Class II devices require Premarket Notification (**moderate risk**)
 - ▶ 3. Class III devices require Premarket Approval. (**high risk**)

REGULATION IN INDIA :

- ▶ In India **medical devices** are governed by **CDSCO (Central Drugs Standard Control Organization)** which is regulated by Directorate General of Health Services , Ministry of Health and Family Welfare , Government of India.
- ▶ **CDSCO** is the only government body which regulate the medical devices.
- ▶ Many **committees** had been set up and given their opinion and recommendation , like the Mahelkar Committee – Central Drug Standard Control Organization.
- ▶ All these are now being taken into to form **the Indian Medical Device regulatory Act (IMRDA)**.

IMRDA:

- ▶ **Indian Medical Devices Regulatory Act** come in force **December 31, 2009.**
- ▶ Inputs to be sent to Dr. B Hari Gopal , Adviser Department Technology, New Delhi.

The **composition** of the committee is represented by:

1. Central Government
2. Eminent Jurist
3. Two eminent medical practitioners
4. Two eminent medical technologists
5. Secretary General Quality council

IMRDA - ESSENTIAL PRINCIPLES :

1. Should not compromise health and safety.
2. Design and manufacture of devices must conform with safety principles.
3. Long term safety should be ensured.
4. Benefits of the devices must outweigh any side effects.
5. Medical devices should be useful for the intended purpose.

Will issue :

1. Design and manufacturing requirements.
2. Performance evaluation.
3. Demonstration of device standards , testing and compliance.
4. Regulation of post marketing follow up.
5. Regulation of recalls.
6. Legislate and punishment for non compliance.
7. Principle of safety.

REGULATORY REQUIREMENTS OF MEDICAL DEVICE DISTRIBUTION IN US:

The basic regulatory requirements that manufacturers of medical devices distributed in the U.S. must comply with are:

1. Establishment Registration:

- ▶ Manufacturer/Importers must register their establishment with FDA.
- ▶ Information verified annually between 1st Oct-31st Dec

2. Medical Device listing:

- ▶ Manufacturers must list their devices with the FDA with information about manufacturer, distributor, specification, accessories/component, remanufacturer, US manufacturer of 'export only' devices.

3. Premarket notification:

Letter of substantial equivalence from FDA required before commercial distribution.

4. Premarket approval (PMA):

- ▶ **Class III devices** are high risk devices so that include the submission of clinical data to support claims made for the device.

5. Investigational device Exemption (IDE) :

- ▶ Allows the investigational device to be used in a clinical study in order to collect **safety and effectiveness data** required to support a **Premarket**.
- ▶ Clinical studies with devices of significant risk must be approved by FDA and by an Institutional Review Board (IRB) before the study can begin

6. Quality system regulation (QC)/ Good Manufacturing Practice (GMP):

- ▶ Includes methods, facilities and controls used for: designing, purchasing, manufacturing, packaging, labeling, storing, installing and servicing of medical / devices to assure compliance.

7. Labeling:

- ▶ Includes labels on the device as well as descriptive and informational literature that accompanies the device.

8. Medical Device Reporting (post marketing):

- ▶ To **detect and correct problems** in a timely manner and to **identify and monitor significant adverse events** involving medical devices.

- ▶ For pre-market and post-market regulation of combination product and medical device, regulatory investigational application should include all information on the entire combination product and device including the details on the drug and device that typically would be submitted in an **IND**.
- ▶ The US FDA **Office of Combination Products (OCP)** is a statutorily mandate office for regulatory affairs in combination product.

The role of the OCP is as follows:

- ▶ 1. Classifies and assigns therapeutic products
- ▶ 2. Coordinates and oversees regulation of combination products
- ▶ 3. Facilitate meetings between sponsors and review staff
- ▶ 4. Help resolve product class and product specific combination product concerns
- ▶ 5. Help resolve disputes between Centers or with sponsors

US FDA uses three key concepts in the regulation of combination products:

1. Constituent parts retain regulatory status and duties
2. Combination products are a **distinct regulatory class**
3. Comprehensive, effective oversight without undue redundancy

The **Conformity Assessment** is done by the **US FDA Centers** :

1. Based on Safety and Effectiveness—constituent parts & interaction of constituent parts
2. Combined/coordinated analysis and decision-making by Centers, with OCP input as needed
3. Varying pathways to market depending on technology and PMOA (primary modes of action, assigned lead center)
4. Consistent procedure and standards to review process.

- ▶ There are **only 14 medical devices** regulated by Drug Controller General of India (DCGI).
- ▶ Currently, a number of specific medical devices are **regulated as drugs** and fall under India's **Drugs and Cosmetics Act (DCA)**.
- ▶ Since 2008, both the Indian Department of Science and Technology and the Ministry of Health have sought to completely **restructure the regulations for medical devices**.
- ▶ Department of Science and Technology : proposed creation of a **Medical Devices Regulatory Authority** that would operate similar to a division within the **CDSCO (Central Drugs Standard Control Organization)** .
- ▶ Ministry of Health: proposed revision of the DCA that would create a **Central Drug Authority** to function similarly to the U.S. FDA.

- ▶ The **CDSCO** is continuing to entrench its own medical device regulation standards. In June 2009, it seemed as if the CDSCO would begin its own form of medical device regulations.
- ▶ CDSCO: released schedule M-3 which provided an official definition for medical devices, outlined a four level medical device risk classification scheme, created a body within the CDSCO to regulate medical devices in India.
- ▶ Ministry of Health and Family Welfare, Government of India, with WHO funding, initiated a country wide National Pharmacovigilance Program.
- ▶ Central Drugs Standard Control Organization (CDSCO), New Delhi, coordinates the program. The Honorable Minister of Health, Dr. Anbumani Ramadass at New Delhi, officially launched the program on November 23, 2004.

REFERENCES:

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3. <https://www.fda.gov/combination-products>
4. <https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/overview-device-regulation>