

*CMC, Post Approval and  
Regulation*

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## Regulatory Affairs



## Regulatory Affairs

- ▶ Plays the pivotal role in **development, licensure, manufacturing and ongoing marketing** of pharmaceutical product.
  
- ▶ RA is a ***discipline and strategic function within the overall organizational structure of a pharmaceutical company that directly interacts with government regulatory agencies concerning regulatory affairs.***

## Role of Regulatory Affairs

Registration documents to regulatory agency.

To keep track on every change in legislation

To give strategic & technical advice to R&D, Production & QC Dept.



## Chemistry, Manufacturing and Control (CMC)

- ▶ CMC Regulatory Affairs is a specific area with RA that has ultimate responsibility for providing CMC regulatory leadership and strategy required to achieve regulatory approvals.
- ▶ CMC RA provides knowledge, understanding, interpretation and utilization of regulatory guidance and regulations, as well as industry and government agency best practice and trends.
- ▶ CMC RA is a high value-added function within a company that is critical to successful development, registration, approval and life cycle management of pharmaceutical product.

**Example:** CMC regulatory submission may contain information associated with API and the finished dosage form, including:

- Names and location of manufacturing and testing sites
- Characterization of the API and composition of the dosage form
- Raw materials used to manufacture the API and finished dosage form
- Description of the product and process development
- Description of the manufacturing process
- Analytical methods and specifications used for testing and release of raw materials, in-process controls, container and closure system, API and dosage form.
- Quality testing, bio equivalence testing
- Release and stability testing data for both API and the dosage form.





# Post approval Regulatory Affairs

- The FDA may require a post-approval study at the time of approval of a Premarket Approval (PMA), Humanitarian Device Exemption (HDE), or product development protocol (PDP) application to help assure continued safety and effectiveness (or continued probable benefit, in the case of an HDE) of the approved drug product of medical device.
- A sponsor's failure to comply with any post-approval requirement may be grounds for withdrawing approval i.e. whether the post approval study will be terminated or revised/replaced.

The safety surveillance is designed to detect any rare or long-term adverse effects over the much larger population and longer time period. Harmful effects shown in this trial may result in drug ban or restricted in certain usages.

## Post-Approval Studies

- Drug-drug interactions
- Drug-food interactions
- Drug-herbal interactions
- Pharmacoeconomic
- Expanded safety/efficacy
- Additional indications
- Strategies for minimization of adverse effects
- Strategies for dose-individualization
- Optimization of surrogate lab tests
- Special populations
- New formulations

## Regulation for combination product & medical devices

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)

- ▶ **Medical Devices** are instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory.
- ▶ Medical devices **does not achieve its primary intended purposes through chemical action within or on the body** of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.
- ▶ 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)

## Device Regulation

- 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)
  3. Class III devices require Premarket Approval. (high risk)

- ▶ 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 1<sup>st</sup> Oct-31<sup>st</sup> 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 they 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 mandated 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 has **three key concepts** it uses 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**

► **Pre-market review process:**

1. Based on safety and effectiveness – constituent part and interaction in between
2. Combined analysis and decision by center
3. Consistent procedure and standards review process

► **Marketing Application:**

1. 1 application research required prior marketing
2. Ongoing reliance on proprietary data
3. Appropriate coordination of post marketing changes to constituent parts

**► Example 1:****Scenario:**

1. Drug X is a topical cream approved to treat disease A.
2. Device Y is a light source cleared for a different use
3. New combination product combines Drug X with Device Y for photodynamic treatment to enhance drug effect for treatment of disease A

**Data needs:**

1. Do not need to reprove that Drug X treats disease A
2. No need to show that Device Y can activate Drug X and to determine what, if any, dose changes are needed to ensure safety and effectiveness of combined use to treat disease A.

■ **Example 2:**

**Scenario:**

1. Investigational combination product combines an investigational topical cream Drug X with Device Y for photodynamic treatment for treatment of disease A

**Data needs:**

1. Need to prove that Drug X treats disease A
2. Need to show that Device Y can activate Drug X and determine appropriate dose to ensure safe and effective combined use to treat disease A.

## References:

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Thank  
you.

