

# Case Study: Global Regulatory Pathways for Registration of a Combination Product

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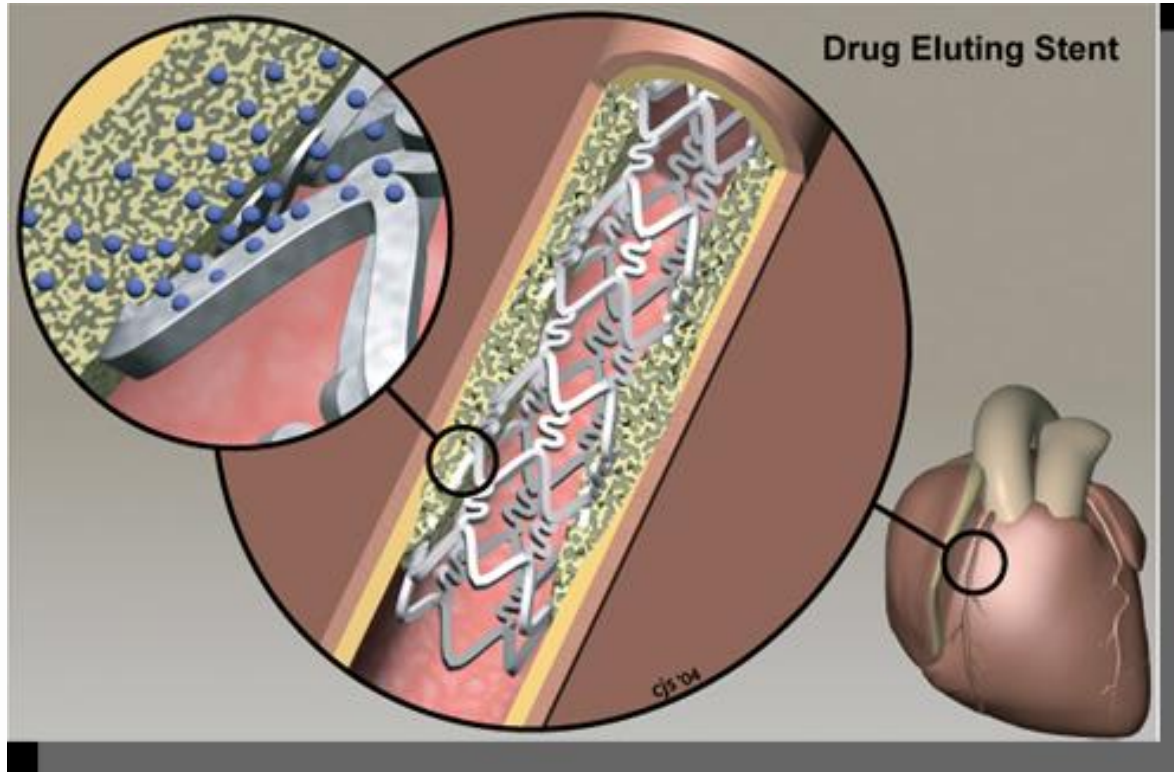
# Contents

- Combination Products
- Case Study: Drug Eluting Stents
- European Law
- US law
- Requirements in:
  - Asia Pacific: China, Japan and India
  - Australia, Canada, United Arab Emirates
  - Latin America: Brazil, Argentina, Mexico
- Conclusion

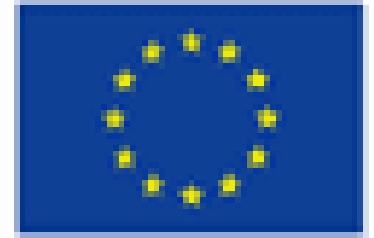
# Is it a Combination Product?

Australia	Not defined as a separate product. CPs regulated according to main function/purpose of the CP.
Canada	A therapeutic product that combines a drug and a device component (which by themselves would be classified as a drug or device) such that the distinctive nature of the drug component and device component is integrated in to a singular component
Japan	No specific definition. CPs are regulated according to main function/ purpose of the CP.
EU	No general definition of combination product
US	Product comprised of two or more regulated components that are physically, chemically or otherwise combined or mixed and produced as a single entity or co-package or as cross-labelled product

# Case Study: Drug Eluting Stents



# European Union



## MDD – Article 1.4

All devices incorporating as an integral part a substance which, if used separately, can be considered to be a medicinal product as defined in Article 1 of the Directive 2001/83/EC, and which is liable to act on the human body with action ancillary to that of the devices, shall be assessed and authorized in accordance with MDD

**The primary mode of action is physical: a device.**

The entire device must be assessed by a Notified Body

# Regulatory route – the device part of the stent

Fulfillment of :

- Essential requirements
- Harmonised standards
- Design Validation and verification
- Clinical Data – Clinical trials or literature review
- QMS
- PMS

# Regulatory route – the drug part of the stent

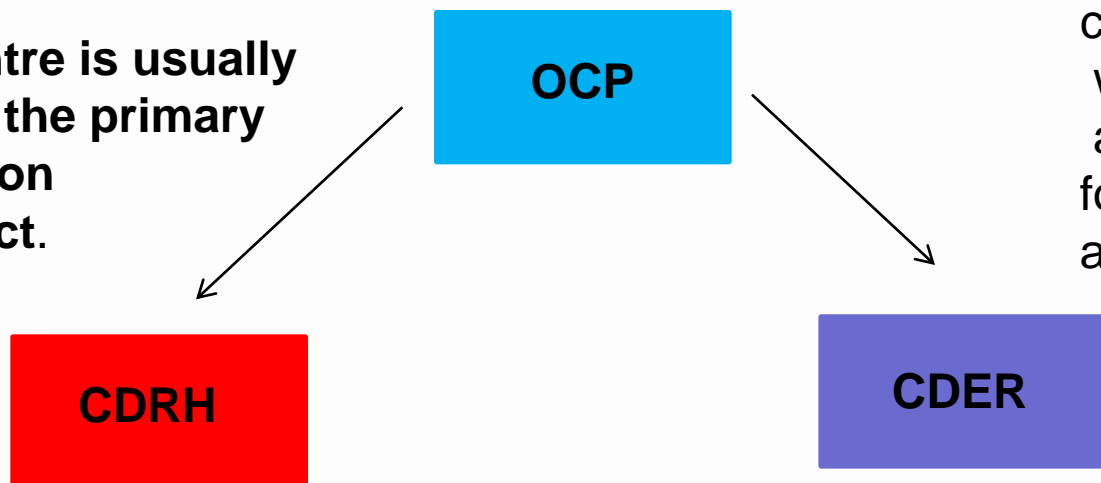
- Manufacturer needs to provide:  
Data regarding the quality, safety and effectiveness of the substance including the clinical benefit/risk profile of the incorporation of the substance into the device
- The Notified Body will attain:  
Scientific opinion from one of the Competent Authorities of the EU or from European Medicines Agency (EMA) with regards to the usefulness of the substance as part of the medical device

# USA



Combination Products in the United States are managed through the Office of Combination Products (OCP) and classified by primary mode of action.

**The lead centre is usually assigned by the primary mode of action of the product.**



The product's components will be reviewed by appropriate centers following respective approval processes.

# Distribution in other countries

- Local Ownership e.g. Japan MAH
- Local Representation e.g. Australia
- Traditional distributorship e.g. Indonesia

# Regulations for Combination Products

The differences in current regulations and regulatory body structures require that manufacturers be prepared to follow varying regulatory pathways in different regions:

In general these are defined by the primary mode of action (Europe, USA) but country specific differences exist .....

# China

**SFDA**  
www.sfda.gov.cn

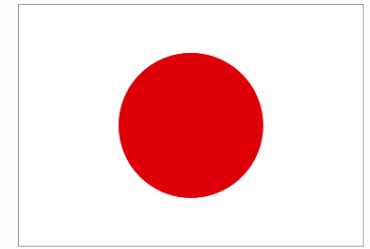
State Food and Drug Administration, P.R. China



Registration of products involves:

- Applications in Chinese and English
- The certificate issued by the government agency of the Country of Origin to authorize the Manufacturer to engage in the production and distribution of medical devices
- In the case of combination products: approval of the medicinal element of a combination product in the Country of Origin is required before submission in China.
- Both drug and device elements of a combination product are clinically evaluated, reviewed and approved in the combined form.
- Clinical Trial Data required for Class II & III products

# Japan



A combination product is judged by its primary mode of action on a case by case basis.

In the case that product is considered a Medical Device, Office of Medical Device leads

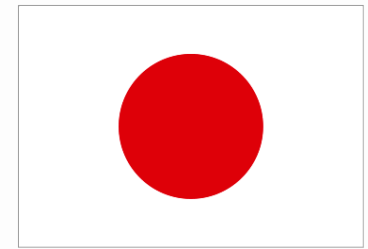
If the product contains a drug – the Office of New Drug participates and the two offices work together in the approval of the medical product.

Quality system: GMP inspection, certification

PMS requirements

Adverse event reporting

# Japan



## **Boston Scientific's Taxus stent clears Japanese regulatory approval March 2, 2009 (CE marked in May 2007)**

Natick medical device leviathan's Taxus Liberte drug-eluting stent approved for sale in Japan.

[Boston Scientific Corp.](#)'s Taxus Liberte drug-eluting stent was given regulatory approvals in Japan, clearing the way for its appearance on the Japanese market.

The [Natick medical device leviathan](#) said [March 3](#) that its paclitaxel-eluting coronary stent system was approved Jan. 28 by Japan's Ministry of Health, Labor and Welfare. Reimbursement was granted March 2 by the country's National Health Insurance System.

About 1,300 medical centers perform cardiac catheterizations in Japan, implanting an estimated 200,000 coronary stents annually, according to Boston Scientific.

# India



## Central Drugs Standard Control Organization

Medical Devices regulated under the Drugs and Cosmetics Act and Rules

At submission:

- Power of Attorney: Authorisation by a manufacturer to their Agent in India.
- Certificate of Free Sale
- ISO 13485 certificate of foreign manufacturing site
- CE Full Quality Assurance Certificate
- CE Design Certificate
- Declaration of Conformity
- Copy of latest Audit Report

# India



## Central Drugs Standard Control Organization

At submission - provide:

**Device Master File (in English)**

**Approval received in other regulatory regions (eg USA; Canada, Japan)**

**Medicinal substance**

- **Information on the identity and source,**
- **Intended reason for its presence,**
- **Safety and performance**

# Australia



Australian Government  
Department of Health and Ageing  
Therapeutic Goods Administration



**Close similarity of the Australian requirements to the European requirements  
Mutual Recognition Agreement (MRA) in place  
Follows GHTF rules – Essential Principles**

Must be registered on Australian Register of Therapeutic Goods (ARTG)

At submission:

Certificate of Free Sale

ISO 13485 certificate of foreign manufacturing site

CE Full Quality Assurance Certificate

CE Design Certificate

Declaration of Conformity

Copy of latest Audit Reports and close out of non conformities

# Canada

Health Canada



Has Mutual Recognition Agreements with the European Union/EEA and Switzerland  
Adopted ISO 13485  
Classification based on EU and US rules

## Requires:

- Establishment License: Office or distributor has to be based in Brazil
- Device license required to sell or advertise medical devices
- Information if the device contains a drug
- Evidence of safety and effectiveness
- Attestation of drug quality, safety and effectiveness
- Vigilance reporting (in line with EU rules)

# United Arab Emirates



- Importer /Distributor is required
- Follows EU rules for classification
- Medicinal substance reviewed by Drug Control Dept of Ministry of Health
- Quality System: ISO 13485 or GMP – certificates attested and authenticated
- Design certificates CE or from, other regulatory authorities
- Human Clinical Data – literature review or investigation
- PMS and adverse event reporting

# Argentina



Technical information documents must be legalised by Argentine Consulate  
Must show conformity with the Mercusor Technical Regulations

Classification based on EU rules but close links with US regulations

Recognises ISO standards eg ISO 14971

Requires:

- Office or distributor must be registered with ANMAT to import product
- Certificate of Good Manufacturing Practise
- Declaration of Conformity according to Mercusor Rules
- Certificate of Free Sale

# Brazil



Agência Nacional de Vigilância Sanitária



Classification based on EU rules

Accepts US product standards and certification by US testing houses

Requires:

- Office or distributor has to be based in Brazil
- Must be registered with ANVISA to import product
- Certificate of Brazilian Good Manufacturing Practise
- Clinical trials for innovative devices
- PMS and adverse event reporting
- Adopted ISO 14971
- Declaration of Conformity according to Mercusor Rules
- Certificate of Free Sale

**Regulations are currently under review**

# Mexico



Majority of imports from the US; part of the North American Free Trade Agreement

Requires:

- Office or distributor based in Mexico
- Must be registered with Mexican Secretariate of Health
- Documents and certificates demonstrating Good Manufacturing Practise
- Risk Management
- Technical and scientific information to attest the safety and efficacy of device
- Vigilance system
- Certificate of Free Sale

# Other Examples

## Singapore – Biomatrix stent

- SINGAPORE, Jan. 18 -- International Group, Ltd. (Biosensors), today announced that the Company has received Conformite Europeenne (CE) Mark approval for its BioMatrix(R) drug-eluting stent system, enabling commercialization of this product in the European Union and the countries in Asia and Latin America that recognize the CE Mark.

## India – Infinium Stent

- Paclitaxel Stent gains CE mark
- However - Patent restrictions in most Western countries, US, Canada, Australia, New Zealand, Japan, China, Korea and Russia.

# Main Strategies

- EU CE Mark provides access to EU and other countries accepting CE marking
- US Requirements which requires GMP approval
- Companies must be constantly aware of regulatory requirements of the two halves of the product and this is seen in Global markets such as China
- Drawbacks: Patents restrict the sale of products in global markets

**Thank you for your attention**

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