

## Medical Devices .....

.....it's not as simple as it looks !!!

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## The GHTF economies and Combination products

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## But .....

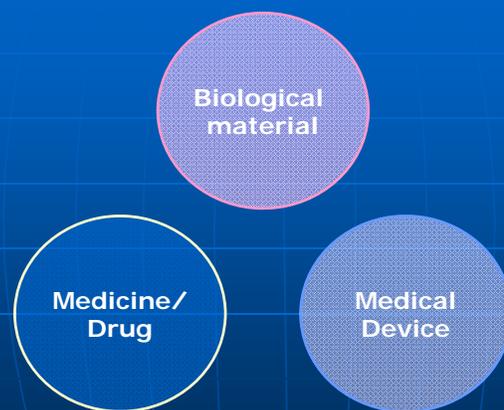
- What is a 'combination product'
- How are they currently regulated
  - EU
  - USA
  - Australia
  - Canada
- What does the proposed ASEAN MDD have to say about 'combination' products



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## Converging medical technologies



Definition of Combination Product	
AUS	Not defined as a separate product. Combination Products regulated according to main function/purpose of the Combination Product.
Canada	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.
Japan	No specific definition. Combination Products are regulated according to main function/purpose of the Combination Product.
US	Product comprised of 2 or more regulated components that are physically, chemically or otherwise combined or mixed and produced as a single entity or co-package product, or as cross-labeled products.
EU	No general definition of combination product. A 'combined advanced therapy product' is defined as one that incorporates as an integral part one or more medical devices, or active implantable medical devices, and viable cells or tissues, or non-viable cells or tissues where the action on the human body of these cells or tissues is primary to the device.

Components of Combination Product	
AUS	<ul style="list-style-type: none"> <li>• Medical Device</li> <li>• Medicine (currently includes biologicals)</li> </ul>
Canada	<ul style="list-style-type: none"> <li>• Device</li> <li>• Drug</li> </ul>
Japan	<ul style="list-style-type: none"> <li>• Device</li> <li>• Drug</li> </ul>
US	<ul style="list-style-type: none"> <li>• Drug</li> <li>• Biological Product</li> <li>• Device</li> </ul> Not Combination Product because combined with: <ul style="list-style-type: none"> <li>• Cosmetics</li> <li>• Foods</li> <li>• Dietary Supplements</li> </ul>
EU	<ul style="list-style-type: none"> <li>• Medical Device</li> <li>• Medicinal Product</li> <li>• Biologic</li> </ul>

<b>Agency Review Determinations – Who is the lead?</b>	
AUS	Consider primary intended purpose and mode of action. May be referred to an internal committee consisting of staff from relevant regulatory areas of TGA.
Canada	MDB – when classified as a Device.
Japan	PMDA leads review – Offices under PMDA will lead depending on how the Combination Product is regarded.
US	Assignment by Office of Combination Product to Agency Center based on "primary mode of action" of Combination Product. If PMOA cannot otherwise be determined, assignment will be based on the following algorithm.  If there is an Agency Center that regulates other Combination Products presenting similar questions of safety & efficacy with regard to the Combination Product as a whole then the Combination Product should be assigned to that Agency Center. If not, the Combination Product will be assigned to the Agency Center that has the most expertise related to the most significant safety & efficacy questions presented by the combination product.
EU	Consider primary mode of action. Opinions must be sought from relevant expert committees for certain Combination Products

<b>Pre-market Review of Applications for Combination Product</b>	
AUS	<ul style="list-style-type: none"> <li>• None unique to Combination Product               <ul style="list-style-type: none"> <li>• Prescription Medicine Applications</li> <li>• Medical Device Applications</li> <li>• Non-Prescription Medicine Applications</li> <li>• Complementary Medicines Applications</li> </ul> </li> </ul>
Canada	<ul style="list-style-type: none"> <li>• Application for Combination Product</li> </ul>
Japan	MHLW defines primary mode of action based on rational provided by company
US	<ul style="list-style-type: none"> <li>• None unique to Combination Product               <ul style="list-style-type: none"> <li>• PMA</li> <li>• 510(k)</li> <li>• HDE</li> <li>• BLA</li> <li>• NDA</li> <li>• ANDA</li> </ul> </li> </ul>
EU	<ul style="list-style-type: none"> <li>• None unique to Combination Product               <ul style="list-style-type: none"> <li>• Medicinal product Applications (which include Advanced Therapy Products)</li> <li>• Medical Device Applications.</li> </ul> </li> </ul>

	Agency “Non-primary” Component Consultations
AUS	According to TGA algorithm
Canada	Joint review with other Health Canada components.
Japan	All handled within MHLW
US	According to Agency SOP governing consultative/collaborative review process.
EU	Notified Body is required to consult the appropriate Drug Authority (National or EMEA). Opinions from Expert Committees may be required.

# The Proposed ASEAN MDD and Combination Products



## From the ASEAN MDD ...

**Medical device** means any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent **and** calibrator, software, material or other similar or related article:

- intended by the **product owner** to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:
  - diagnosis, prevention, monitoring, treatment or alleviation of disease,
  - diagnosis, monitoring, treatment, alleviation of or compensation for an injury,
  - investigation, replacement, modification, or support of the anatomy or of a physiological process,
  - supporting or sustaining life,
  - control of conception,
  - disinfection of medical devices,
  - providing information for medical or diagnostic purposes by means of *in vitro* examination of specimens derived from the human body;

and

- which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means.



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## Intended primary mode of action

### Drug eluting stent



- **Primary intended mode of action**
  - stent opens artery
- **Secondary action**
  - drug reduces inflammation and restenosis of artery
- **Regulated as a device**

### Drug eluting disc

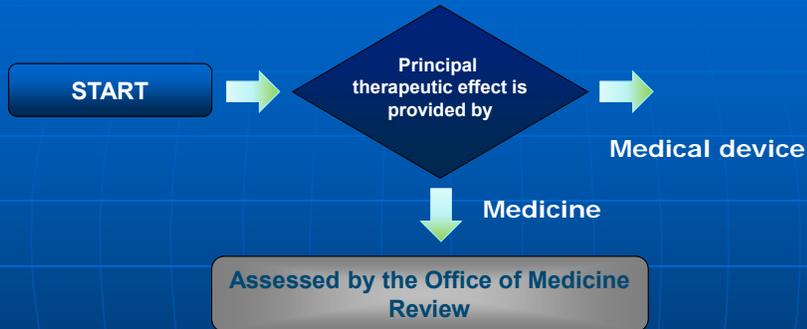


- **Primary intended mode of action**
  - chemotherapy for brain tumour
- **Secondary action**
  - local delivery of drug by device
- **Regulated as a drug**



Source: S. Alpert, M.D., PhD. (Medtronic, Inc.). Asian Harmonization Working Party, Seoul, Sept. 2006 (adapted)

## The TGA Process .....



- **Principal therapeutic effect** is usually self evident
  - Mode of operation claimed by the manufacturer
  - Clinical Evidence
- Internal Committee to decide when doubts exist



## The TGA Process .....



Pharmaceutical Chemistry Review

Medicines Evaluation

Toxicology & Pre-clinical  
Pharmacology Review

Medicines Evaluation

Clinical Data Review

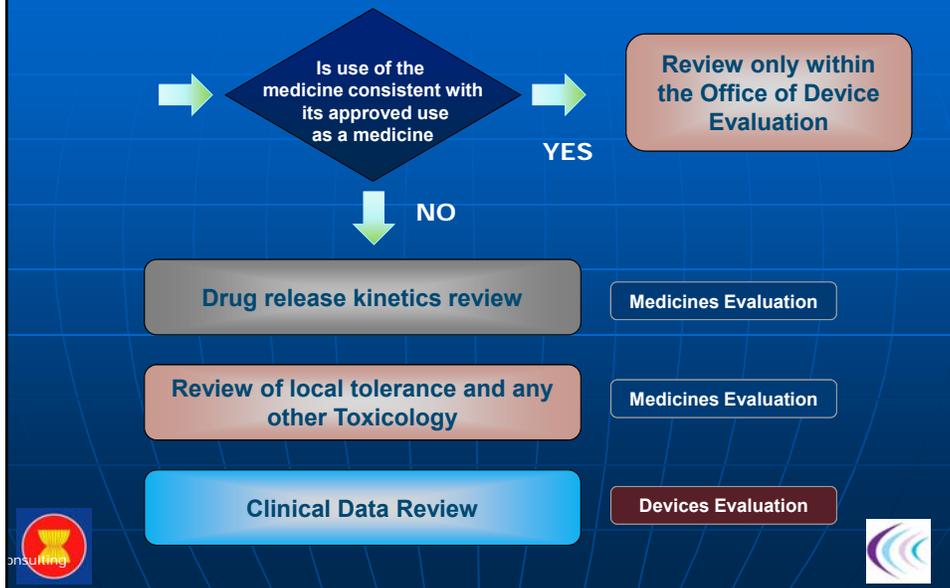
Devices Evaluation



## The TGA Process ....



## The TGA Process ....



## The TGA Process .....

- For medical devices incorporating a medicine acting in a manner **ancillary** to that of the device .....
- The more the medicinal substance, its use and its manufacturer are known to the TGA, the less the requirement for evaluation or consideration by an expert committee outside the device program



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For substances that would normally be a prescription medicine .....

:

- a new chemical entity will go through the full medicine evaluation process, including consideration by the Australian Medicines Advisory Committee (AMEC) prior to consideration by the Medical Device Advisory Committee (MDAC).



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For substances that would normally be a prescription medicine .....

:

- a medicine already on the ARTG, but from a new manufacturer, will be treated as a new generic and an evaluation of the Drug Master File is required (covering toxicology and pharmaceutical chemistry aspects).



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For substances that would normally be a prescription medicine .....

:

- an approved medicine for which the device application involves a new indication, will undergo clinical assessment within the device program and the application will be referred to the drug evaluation area for pharmaceutical chemistry aspects.



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## Conclusions

- Definition of “medical device” is essential in defining “border lines” between regulated products and systems
- Demarcation lines may be subtle  
Guidance documents are important
- Definition turns on primary intended mode of action
- Determination depends on manufacturer claims
  - Justified and consistent with scientific evidence
- Determines regulatory framework and requirements
  - Requirements should not be applied cumulatively
- Opportunity for international harmonisation



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