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Bocconi School of Management

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REGULATION AND HTA OF MEDICAL DEVICES IN EU: WHAT CAN WE LEARN?

Rosanna Tarricone, PhD

Associate Dean, Government Health and Non Profit Division

Issue Panel "Opportunities and challenges in international harmonization of HTA of medical devices - gaps between European and Asian countries" ISPOR Tokyo Sept 8th-13th 2018

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Premise

1. Current regulatory systems aim at assessing safety, performance and – sometimes – efficacy of medical devices
2. Health technology assessment (HTA) aims at assessing medical devices' effectiveness and to compare its added value against its incremental cost
3. Both processes have been developing fast in terms of requirements, revisions and diffusion, but little convergence has been achieved between the two
4. Manufacturers often need to develop clinical evidence for HTA bodies instead of regulators (i.e. in some European countries) or conversely for regulators and not for HTA bodies (i.e. USA)

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Regulatory requirements in different jurisdictions

- All jurisdictions relate evidential requirements to the level of patient risk associated with the use of different categories of device:

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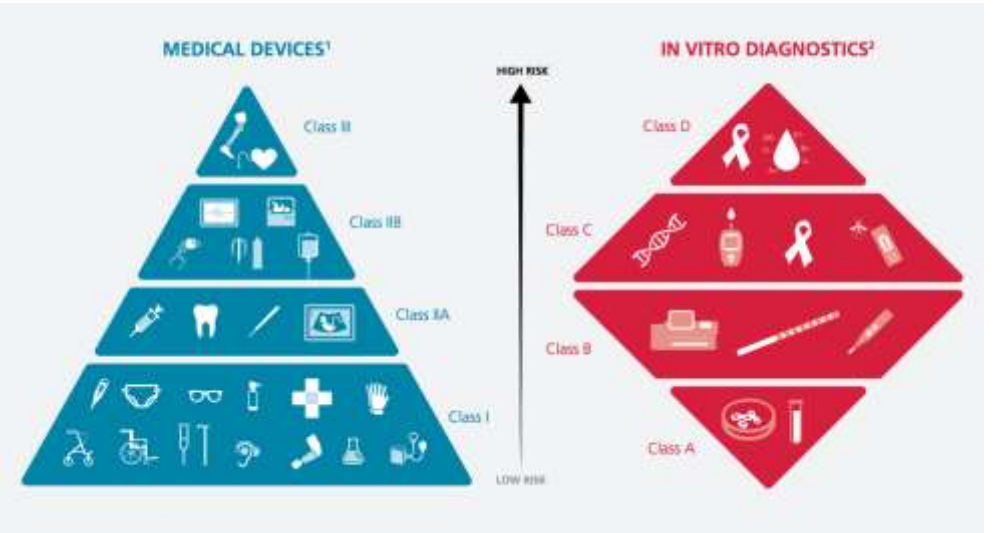
The European risk-based classification system for MD



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The risk-based classification system for MDs in other jurisdictions

Table 1. Device classification in the jurisdictions studied.

Jurisdiction	Classification rules	Class of device	Risk level	Examples of medical devices
EU	Annex IX of the Medical Devices Directive	Class I	Low risk	Stethoscopes
		Class IIa	Low-to-medium risk	Ultrasound scanning
		Class IIb	Medium-to-high risk	x-ray machines
		Class III	High risk	Cardiac stent
USA	FDA Medical Device Classification	Class I	Low risk	Elastic bandage
		Class II	Moderate risk	Infusion pumps
		Class III	High risk or novel	Heart valves
Canada	Canadian Medical Device Regulation	Class I	Low risk	Bandage
		Class II	Low-to-medium risk	Surgical Gloves
		Class III	Medium-to-high risk	Hip Replacement implant
		Class IV	High risk	Implantable defibrillator
Australia	Therapeutic Goods Administration	Class I	Low risk	Surgical microscope
		Class IIa	Low-to-medium risk	Electrical acupuncture
		Class IIb	Medium-to-high risk	External defibrillators
		Class III	High risk	Biological heart valves
		Active implantable medical devices	High risk	Implantable pacemaker
Japan	Japan Pharmaceutical Affairs Law and Japanese Medical Device Nomenclature code	Class I	Low risk	Scalpel
		Class IIa	Controlled	Ultrasound scanning
		Class IIb	Designated controlled	Electronic endoscopes
		Class III	Highly controlled	Artificial bones and joints
		Class IV	Highly controlled	Pacemakers
Brazil	Annex II of RDC 185/2001	Class I	Low risk	Stethoscopes
		Class II	Low-to-medium risk	Ultrasound scanning
		Class III	Medium-to-high risk	x-ray machines
		Class IV	High risk	Stent implant
China	China Food and Drug Administration Order No. 15 as of 5 April 2000 and other China Food and Drug Administration documents	Class I	Low risk	
		Class II	Moderate risk	
		Class III	High risk	Implant, life support or sustenance

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Regulatory requirements in different jurisdictions

- All jurisdictions relate evidential requirements to the level of patient risk associated with the use of different categories of device:
  - there are differences in the requirements as to the balance **between pre-market and post-market controls**
  - **Existing regulatory processes** for MDs **generate less clinical evidence** than the corresponding processes for pharmaceuticals:
    - **Insufficient clinical evidence relating to the safety and performance of a device before it is placed on the market**
- A challenge in all jurisdictions is in finding the appropriate balance between assessments of efficacy and safety on the one hand and allowing rapid access to patients on the other (e.g. early dialogues such as "EXCITE" in Canada or "SEEED" in EU)

Evidence requirements for pre-market approval

For CE marking for devices in Class III, the manufacturer must conduct some human clinical investigations, but it is not compulsory that these are randomized clinical trials:

- MDs' features often make RCTs unethical, inapplicable or very difficult and too costly (e.g. proven effectiveness, learning curve, incremental innovation)


BMJ

EDITOR'S CHOICE

The scandal of medical device regulation

The breast implant scandal and European Medical Device Regulation

The recent silicone breast implant scandal in Europe has led to questions about whether or not European medical device regulations are sufficient to protect patients not only from unsafe breast implants, but unsafe medical devices in general.

What were the events that led to the discovery of substandard materials being used to manufacture the breast implants?

How are medical devices, specifically, breast implants regulated in Europe?

MEDICAL DEVICES

Europeans are left to their own devices

When it comes to medical devices, Europeans seem to get a worse deal than US patients. Deborah Cohen and Matthew Billingsley compare the regulatory systems

MEDICAL DEVICE REGULATION

How a fake hip showed up failings in European device regulation

Deborah Cohen investigates how EU authorities would be prepared to allow a fake hip prosthesis with dangerous design flaws onto the market

Deborah Cohen investigations editor

MEDICAL DEVICE REGULATION

Faulty hip implant shows up failings of EU regulation

Deborah Cohen describes an investigation showing how a fake hip prosthesis with dangerous design flaws stood to be approved for the EU market

Deborah Cohen investigations editor

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EU New Regulation on MDs

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

(Text with EEA relevance)

Stricter requirements for clinical evidence to support assessments of high risk and implantable medical devices

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EU (proposed) new Regulation on HTA

EUROPEAN COMMISSION

Brussels, 31.1.2018
COM(2018) 51 final

2018/0018 (COD)

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on health technology assessment and amending Directive 2011/24/EU

(Text with EEA relevance)

{SWD(2018) 41 final} - {SWD(2018) 42 final}

- the European Commission has proposed a regulation aimed at centralizing HTA of health technologies through **Joint Clinical Assessments**

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EC Regulation on HTA: scope

HTA domains	
Health problem and currently used technologies	Clinical domains
Description of technology under assessment	
Relative clinical effectiveness	
Relative safety	
Economic evaluation	Non-clinical domains
Ethical aspects	
Organisational aspects	
Social aspects	
Legal aspects	

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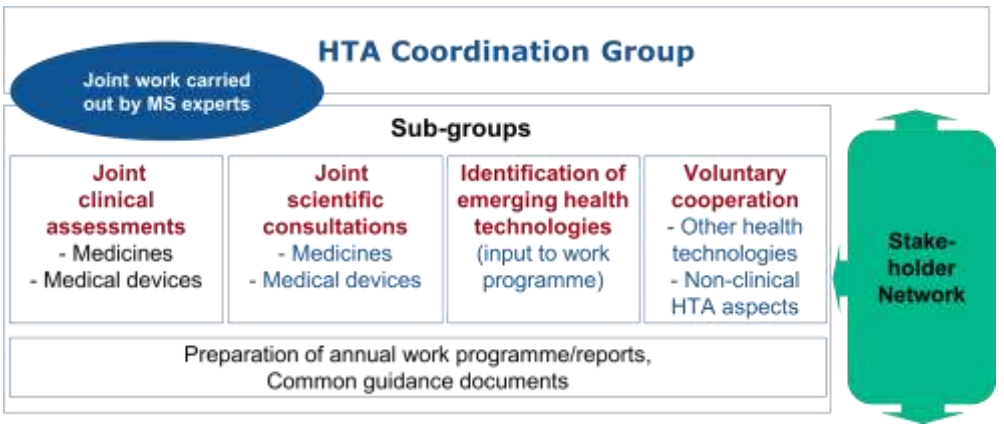
EC HTA Regulation: activities

Article 3



Joint Clinical Assessments: products

Article 5

- **Medicinal products**: centrally authorised new active substances and new therapeutic indications
- **Medical devices**:
  - Medical devices classified as **class IIb and III** pursuant to Article 51 of Regulation (EU) 2017/745 for which the relevant expert panels have provided a scientific opinion in the framework of the clinical evaluation consultation procedure pursuant to Article 54 of that Regulation
  - In vitro diagnostic medical devices classified as class D pursuant to Article 47 of Regulation (EU) 2017/746 for which the relevant expert panels have provided their views in the framework of the procedure pursuant to Article 48(6) of that Regulation
  - Additional selection by HTA Coordination Group based on criteria: Unmet medical needs; potential impact on patients, public health and healthcare systems; significant cross-border dimension; major Union-wide added value

Use of Joint Clinical Assessments

Article 6, Recital 16

Joint clinical assessment – conclusions limited to:

- an analysis of the relative effects of the health technology being assessed on the patient-relevant health outcomes chosen for the assessment
- the degree of certainty on the relative effects based on the available evidence.

NATIONAL

NATIONAL APPRAISAL
of joint clinical assessment and additional context-specific considerations (e.g. number of patients affected in Member State, how patients are currently treated in the healthcare system, costs)

Conclusions on added value
(e.g. added therapeutic value, cost-effectiveness…)

Scope for further harmonisation of standards beyond EU?

- The International Medical Device Regulators Forum (IMDRF) was conceived in February 2011 as a forum to discuss future directions in medical device regulatory harmonization.
- It is a voluntary group of medical device regulators from around the world who have come together to accelerate international medical device regulatory harmonization and convergence.
- The current members are:

1. Australia
2. Brazil
3. Canada
4. China
5. Europe
6. Japan
7. Russia
8. Singapore
9. South Korea
10. United States of America


Current work items

Work Item	Working Group Membership	Coordinator
Unique Device Identification (UDI) Application Guide	Regulatory and stakeholder membership	Coordinator - Salvatore Drabio, European Union
Personalised Medical Devices	Regulator membership	Dr Elizabeth McGrath, Australia
Standards - Improving the quality of international medical device standards for regulatory use	Regulatory and stakeholder membership	Scott A Colburn, USA
Adverse Event Terminology	Regulator membership	Hiroshi Ishikawa, Japan
Good Regulatory Review Practices	Regulator membership	Melissa Torres, USA
Regulated Product Submission	Regulator only and regulator and stakeholder membership	Nancy Shortland, Canada

Closed work items

Work Item	Working Group Membership	Coordinator
Patient Registries	Regulator and stakeholder membership	Denise Martinez-Diablo, USA
Software as a Medical Device	Regulator and stakeholder membership	Bakul Patel, USA
A review of the NCAR system	Regulator membership	Jean-Francois Rouhe, Europe
Medical Device Single Audit Program (MDSAP)	Regulator membership	Kimberly Trautman, USA
IMDRF recognized standards	No Working Group required for initial information gathering phase	Mathias Neumann, Europe
Roadmap for implementation of UDI system	Regulator and stakeholder membership	Laurent Sellos, Europe

Open issues

- Medical Devices have traditionally been placed in therapy with weaker clinical evidence if compared to drugs
- EU has made great efforts to fill the evidentiary gap of MDs and to harmonise the regulation and the HTA requirements but some issues are still to be solved:
  - Clinical evidence is key:
    - Pre-market (e.g. early dialogues)
    - Post-launch (e.g. RWE, see also FDA guidance)
  - Choice of the comparator (e.g. is «standard of care» the same across jurisdictions?)
  - Stakeholders' engagement (e.g. clinicians, managers, patients, industry) is fondamental to develop the relevant data to inform the regulation processes but is still unclear how
  - How these issues relate to the Asian context?

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Panel Issue Speakers

Ataru Igarashi
Associate Professor
University of Tokyo

Sukyeong Kim
Senior Research Fellow
National Evidence-based Health Care Collaborating Agency (NECA)
Seoul SOUTH KOREA