Regulatory Barriers to Translation of Healthcare Technology

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Quick Overview of Device Regulation in the EU

Regulation of healthcare products

- Product must be placed on the market for a **medical purpose**
- Both devices and medicinal products may prevent or treat disease
- Key concepts:
  - **Manufacturer's** intended purpose
  - Primary mechanism of action: IMP vs mechanical
- No "Combination Products" – either MP or MD
- Does not include laboratory or manufacturing equipment

What is a medical device?

Definitions (93/42/EEC) Article 1.2

medical device means any instrument, apparatus, appliance, software, material or other article … intended by the manufacturer to be used for human beings for the purpose of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap

— investigation, replacement or modification of the anatomy or of a physiological process

— control of conception

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

Active implantable medical devices (90/385/EEC)

"Active medical device" = any medical device relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity

"Active implantable medical device" = any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure

Medical Device Directives

- 93/42/EEC - medical devices (MDD)
- 90/385/EEC - active implantable medical devices (AIMDD)
- 98/79/EC - *in vitro* diagnostic medical devices (IVDD)

- Numerous amending directives and updates since originals published
- Major revision – general MDD and AIMDD to be combined and published as a consolidated Regulation; likely to be in force late 2020
- New IVD Regulation

OBJECTIVE: Improved controls and oversight of system

Relevant Agencies for Medical Devices

Competent Authorities

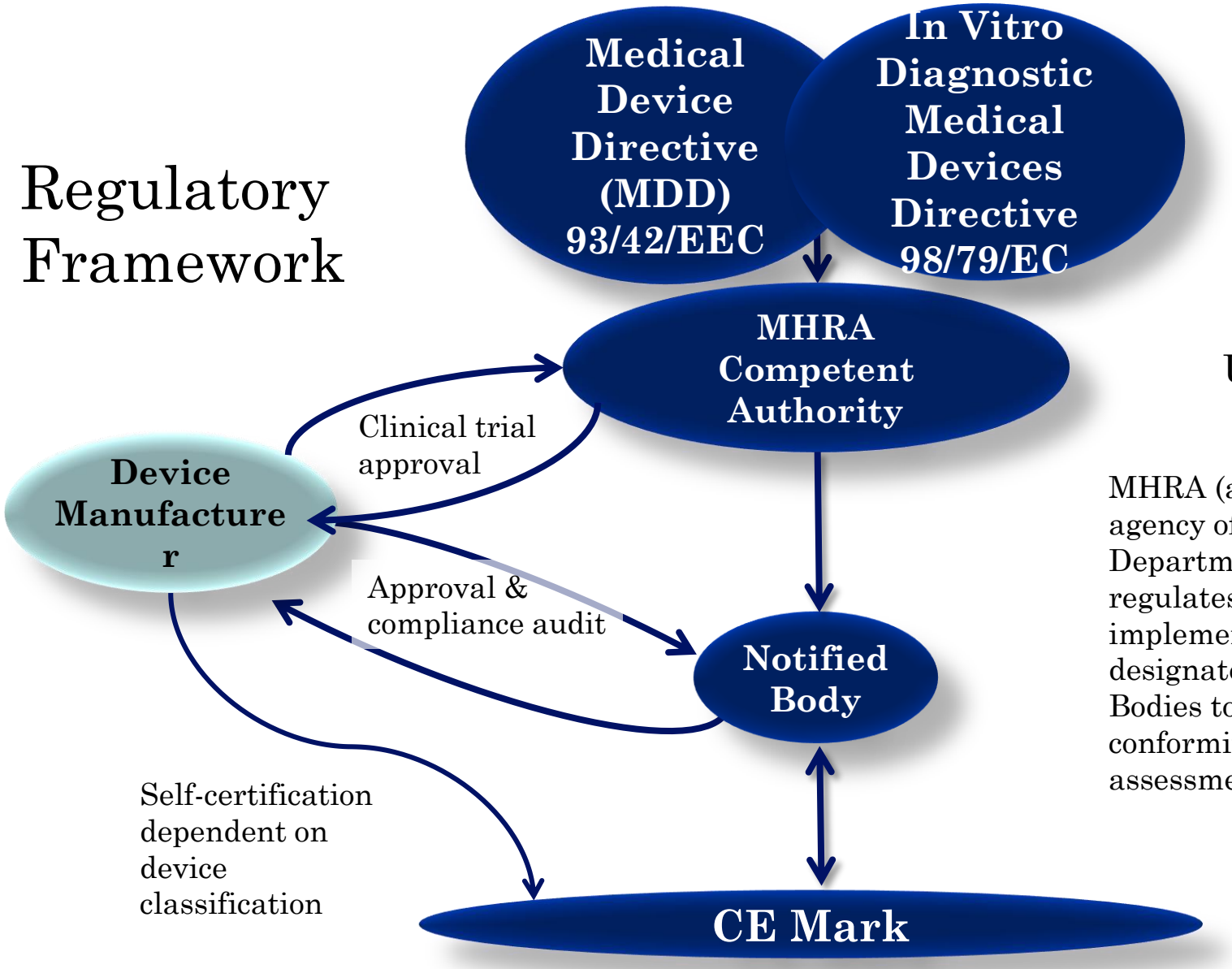
- Act on behalf of the national government to ensure requirements of the MDD are met
- Responsible for
  - transposition of MDD into national law
  - appointment and supervision of Notified Bodies
  - authorisation of clinical investigations of devices
  - post-market surveillance and adverse incident reporting
  - maintaining registration of Class I devices and IVD

Relevant Agencies for Medical Devices

Notified Bodies

- Independent testing or certification body
- Appointed by CA for competence in one or more Conformity Assessment procedures – scope is defined
- May also be certification organisations for quality management and other standards
- Responsible for:
  - Quality System certification
  - Design Dossier certification
  - Type testing and product verification
  - Audit of manufacturers and sub-contractors

Regulatory Framework

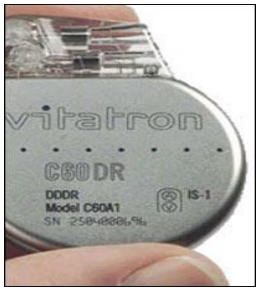


MHRA (an executive agency of the Department of Health) regulates UK Directive implementation designates Notified Bodies to conduct conformity assessments

General principles of device directives

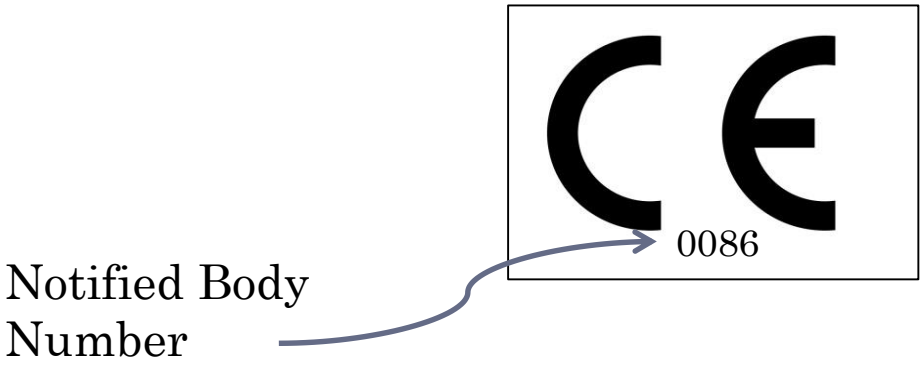
CE

- Establish “Essential Requirements” but don’t set detailed technical obligations
- = “New Approach” directives



CE Marking

- Compliance entails demonstrating conformity with the Essential Requirements relevant to your device
- Compliance with relevant directive(s) is signified by affixing of CE mark on device or its labelling
- CE mark allows freedom to place on the market throughout EU
- Manufacturer's decision and responsibility



Principles of medical device regulation in the EU (1)

- Devices are Class I, IIa, IIb or III
- Classification of device is determined by manufacturer's intended use (some exceptions)
- Device class determines options for "conformity assessment route" by which compliance with the MDD is demonstrated
- Choice of conformity assessment route and determination of compliance is manufacturer's responsibility
- Active implantable medical devices not differentiated by class (separate directive)

Principles of medical device regulation in the EU (2)

- Device class determines level of involvement of NB and CA in device assessment
- Class III devices require prior assessment by a Notified Body
- Additional prior approval by Competent Authorities for devices containing:
  - Medicinal substances
  - Animal-derived materials from TSE-susceptible species
  - Non-viable human tissue (in future under MDR)

Software & Apps

- Software may be an integral part of a medical device (embedded)
- or a medical device in its own right if placed on the market at a separate time/independently from a main device
  - … directly provides a therapeutic or diagnostic purpose or directly influences the use of a medical device
- Software must be validated according to state of the art
- MHRA guidance on Apps [August 2014] https://www.gov.uk/government/publications/medical-devices-software-applications-apps
- EU commission activity:

https://ec.europa.eu/digital-single-market/en/mhealth

Green paper and new working group from March 2016

Essential Requirements

- Risk Management process
- Design, materials and manufacture
- Safety in intended use
- Safety and performance over specified life-time of device
- Risks of side effects/adverse effects must be acceptable when considered against the intended performance of the device
- Clinical evaluation
- Labelling and instructions, warnings and precautions
- MDR – specific new ERs – covers general and AIMDs
  - software
  - programmable devices
  - active implantable devices
  - devices intended for lay persons

Essential Requirement 1 (Safety)

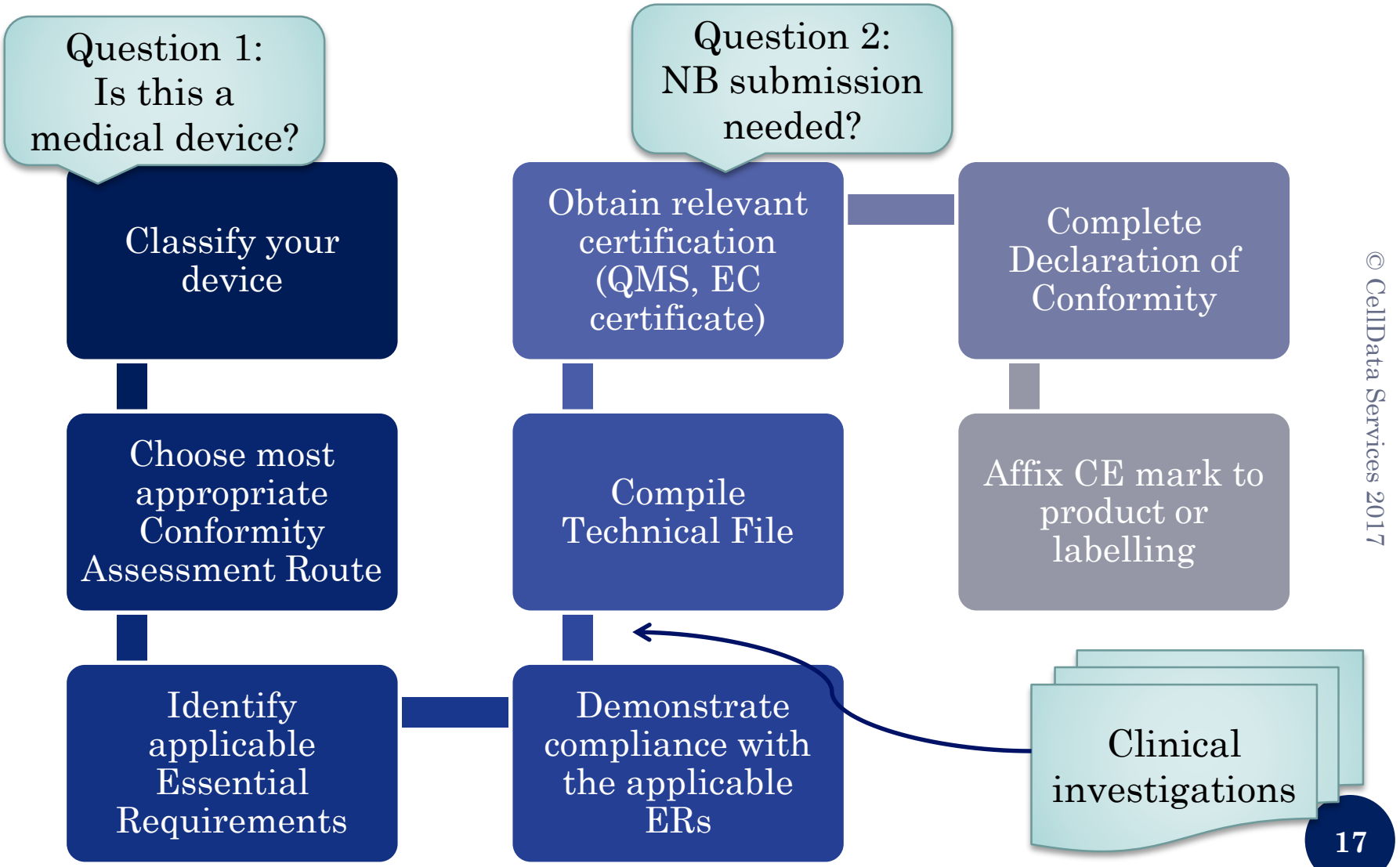
The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their intended use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety

This shall include:

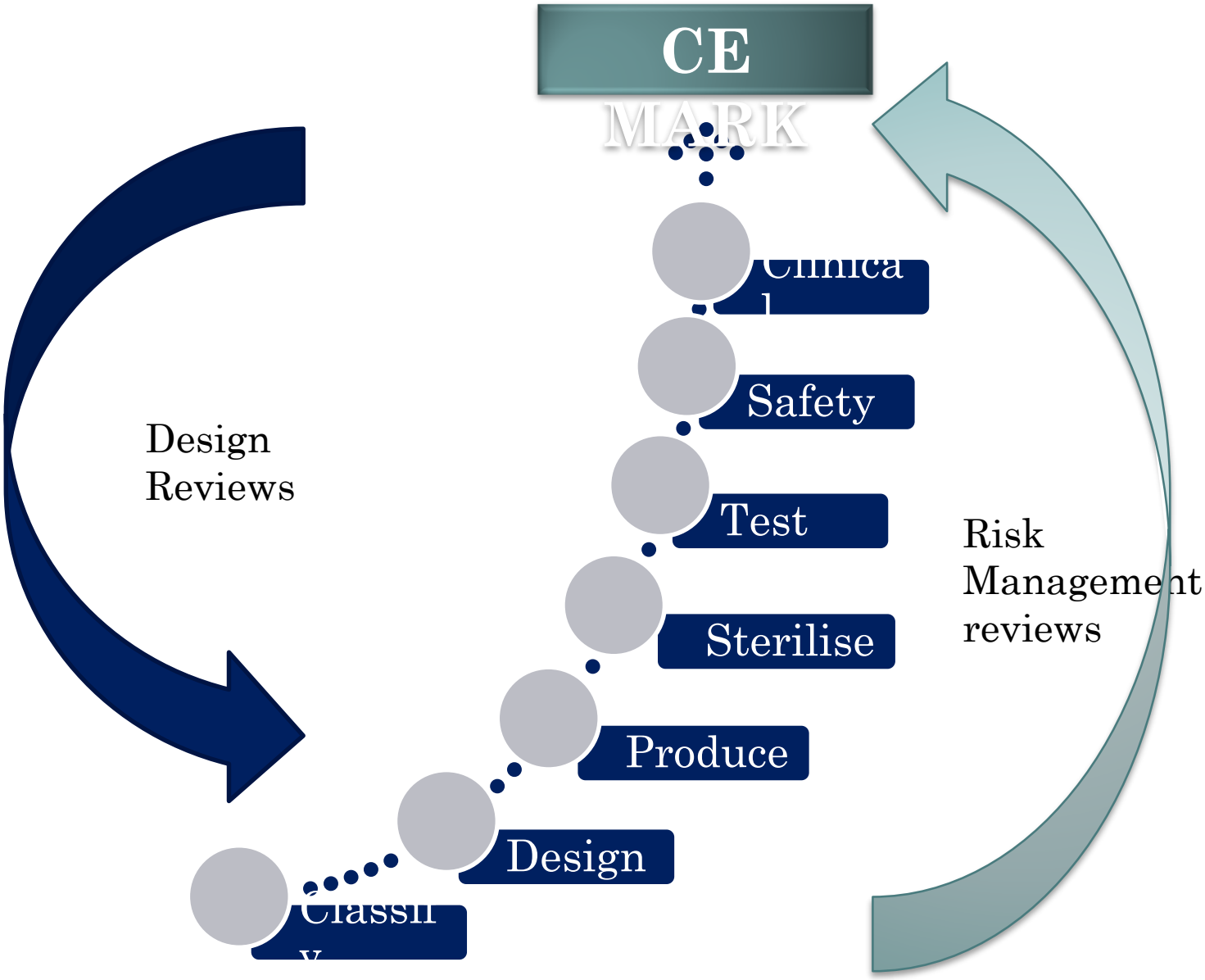
— reducing, as far as possible, the risk of use error due to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and

— consideration of the technical knowledge, experience, education and training and where applicable the medical and physical conditions of intended users (design for lay, professional, disabled or other users)

CE-Marking of Medical Devices – Basic Pathway



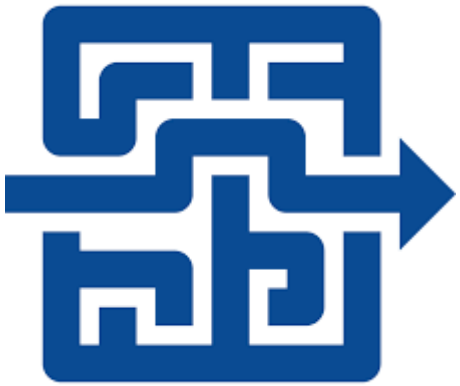
Iterative processes

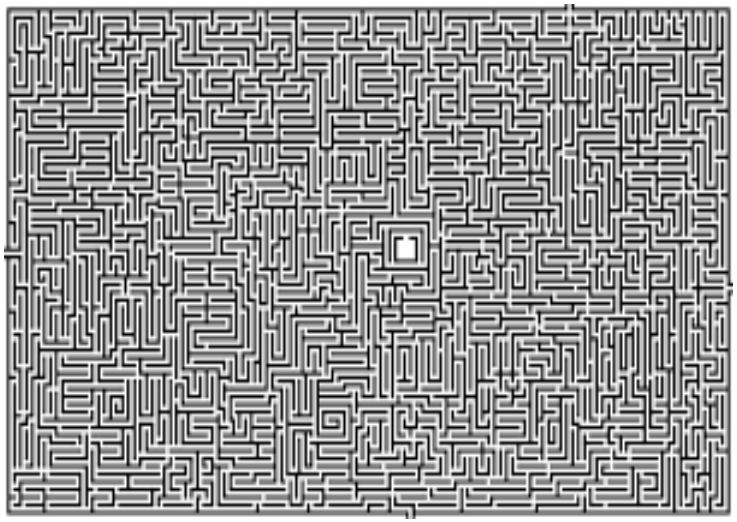


Barriers to Translation

Regulatory issues influencing success

Potential regulatory hurdles





What can hold you up?

Incorrect classification – Example (1)

- Product = sweat card, part of a system intended to measure chloride ions in sweat for the diagnosis of cystic fibrosis.

Sweat stimulated by delivering pilocarpine through the skin to stimulate sweating and measurement of Cl^- in sweat sample. Includes three components:

a) sweat cards: contain pilocarpine and a gel component that collects the resultant sweat

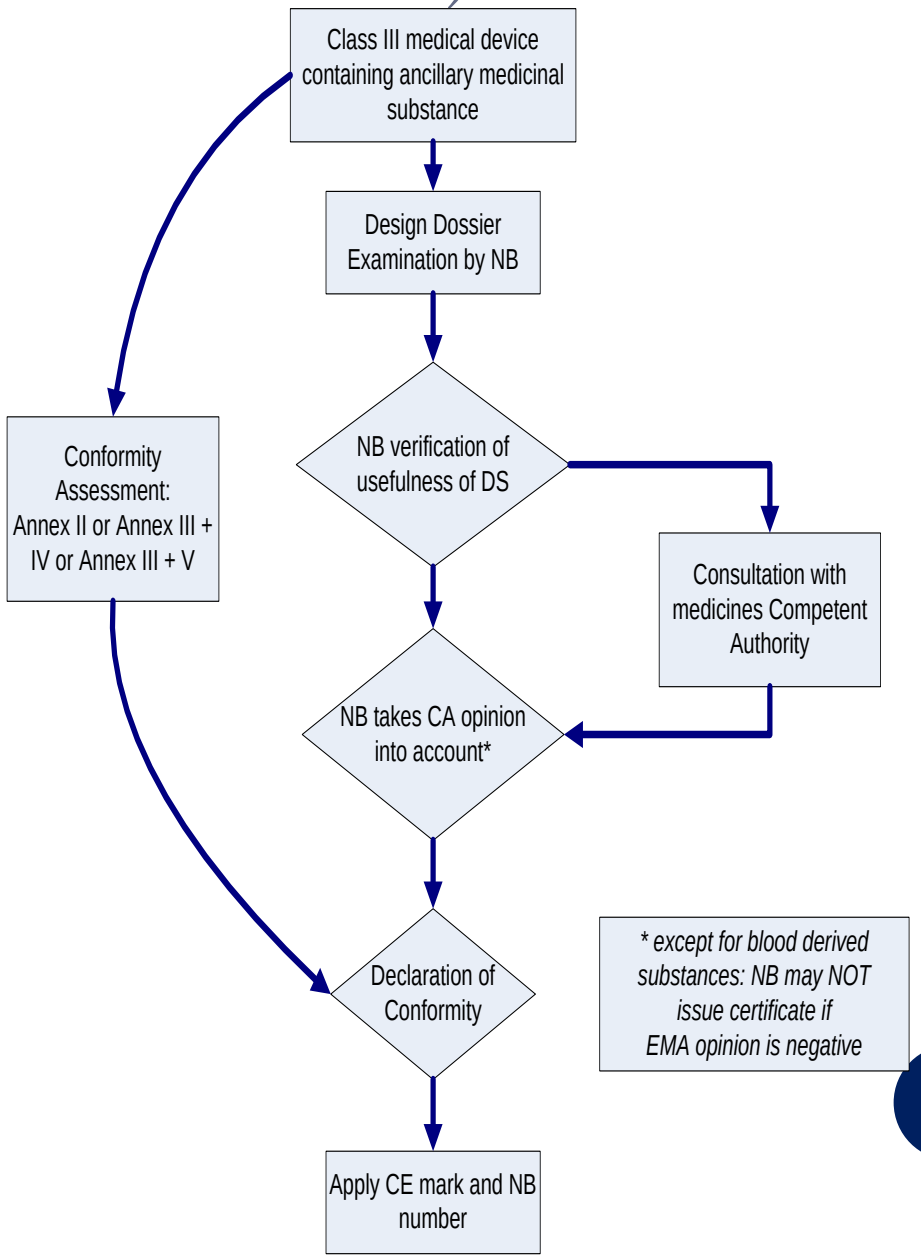
b) remote module: sweat card is inserted into a unit, which is placed in direct contact with skin; unit delivers pilocarpine and resultant production of sweat is collected, analysed and sent to a receiver base

c) terminal or receiver base containing unit for calculation and display of results

- Manufacturer: main purpose of the sweat sensor card is not to elicit a response via a pharmacological action but to diagnose cystic fibrosis by measuring sweat chloride. Pilocarpine iontophoresis is used for stimulation of sweat as a first step and hence the pilocarpine iontophoresis is an ancillary process to collect sweat
- Sweat sensor card is Class IIa

Outcome (Commission MDEG)

- The primary purpose of the sweat card is sweat collection; the pilocarpine is acting in an ancillary manner by stimulating glands to ensure collection of sweat is more effective
- This device incorporates, as an integral part, pilocarpine which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 2001/83/EC, and that is liable to act on the human body with action ancillary to that of the device
- Therefore the sweat cards are in Class III
- Additional drug consultation step
- Full quality and safety data on pilocarpine to medicinal product standards



Classification example (2)

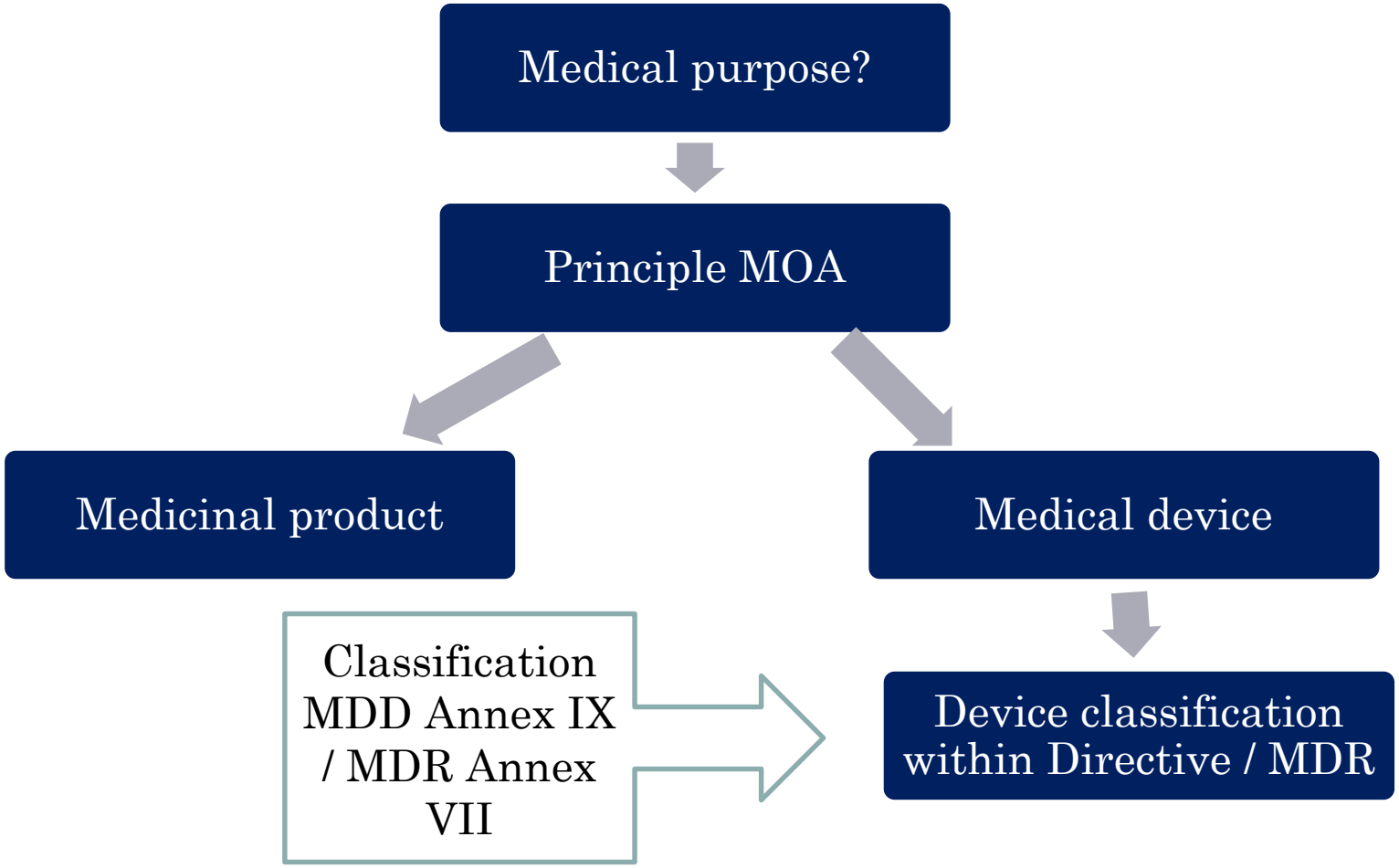
Software application for faster utilisation of an international guideline regarding the Classification of Malignant Tumours (TNM) issued by the UICC (International Union Against Cancer), in the view of classification of cancer by anatomic disease extent.

- Three variables are introduced into the system:
  - tumour size and whether it has invaded nearby tissue (described as T0, T1, T2, etc.)
  - regional lymph nodes that are involved (N0, N1, N2, etc.)
  - metastasis (M0 or M1)
- Based on the selection of these 3 categories/variables, the application indicates the stage of disease development (cancer extent), in accordance with the guideline
- This information software facilitates the search and use of an international guideline which physicians usually consult via electronic file, or in paper format

Device Classification?

- The software does not perform an action on data other than simple search function, as per MEDDEV Guidance 2.1/6
- The product does not therefore fulfil the definition of medical device, according to Directive 93/42/EEC, and should not be qualified as such

Classification – the first hurdle

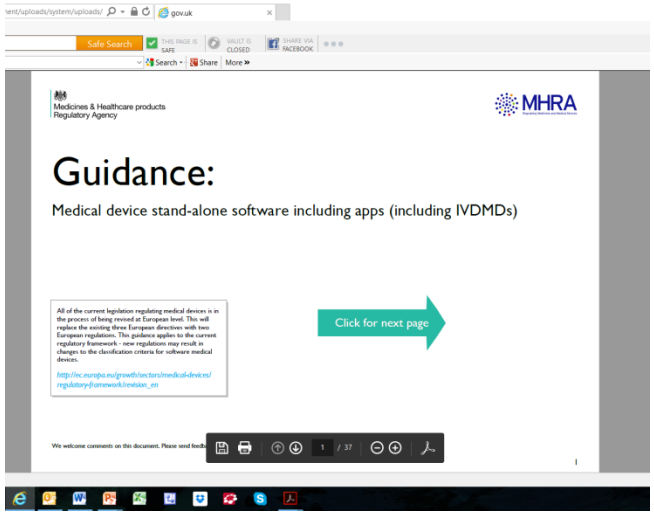


New Concepts

- All regulation of healthcare technology is retrospective
- Can only regulate mature concepts based on CA understanding
- Software
  - Original mention in 93/42/EEC limited
  - Amended by 2007/47/EC to include stand-alone = active medical device
  - MEDDEV 2.1/6 July 2016
- New challenges
  - Increasing complexity: devices & drugs, proteins, antibodies
  - Nano-technology
  - Personalised medicine – eg 3D printing, bioprinting, autologous cell therapies
  - Wearable technology

New concepts

- Competent Authority



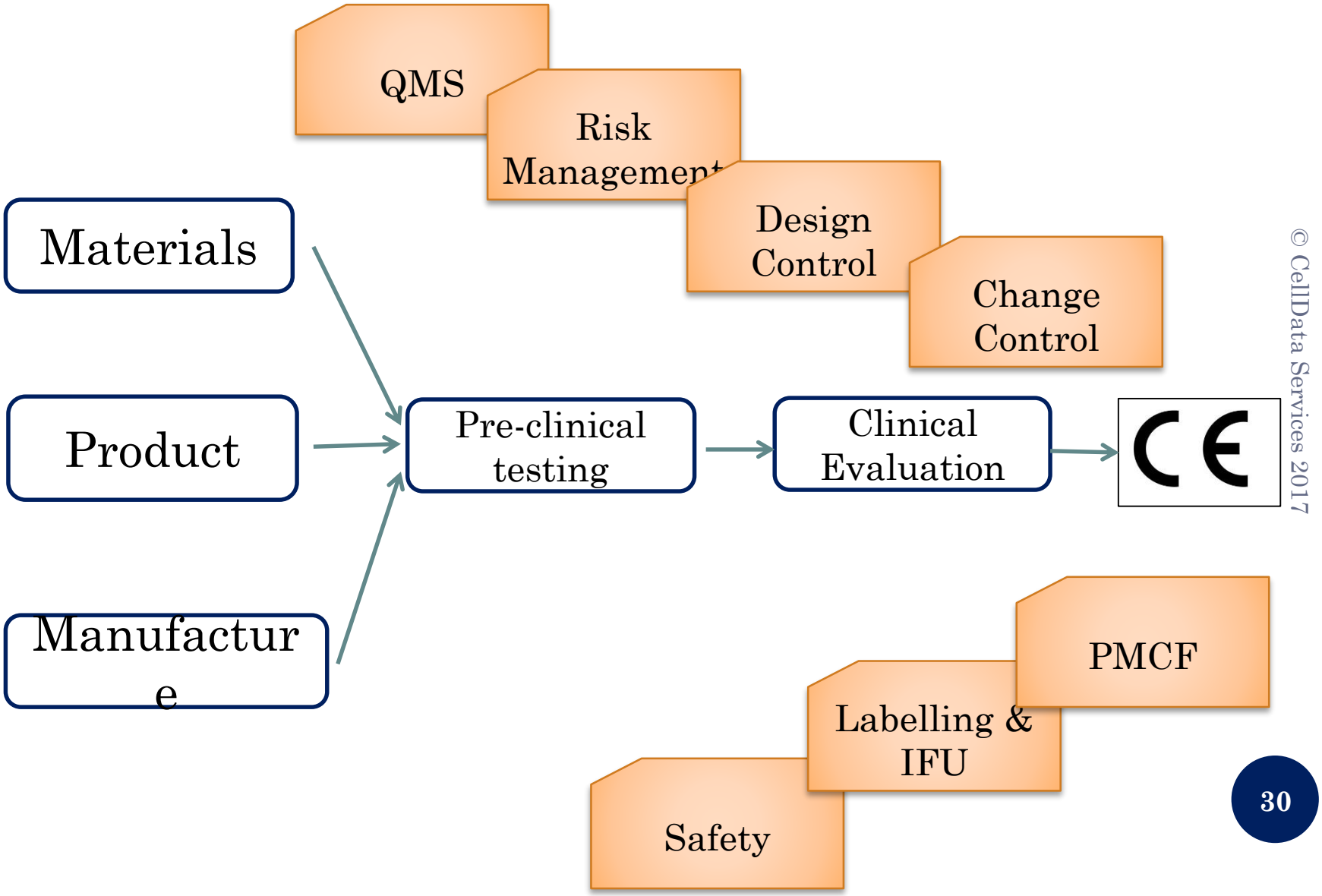
- European Medicines Agency
- ITF
  - nanomedicines
  - pharmacogenomics
  - synthetic biology
  - biomaterials
  - modelling and simulation
  - m-health

- Notified Bodies

New concept?

- Read classification summaries from CAs
- Check MEDDEVs
- Consider parallels to other situations
- Talk to CAs!

COMPLIANCE – THE WHOLE PICTURE



MDD/MDR PLUS…

- Additional legislation may apply
  - Waste Electrical and Electronic Equipment (WEEE) directive 2012/09/EU
  - Restriction of Hazardous Substances in Electronic Equipment (RoHS2) Directive 2011/65/EU
  - Data Protection Regulation (EU) 2016/679

Funding

- Funding via grant – distortion of processes
- Grant for specific end-point, eg clinical proof-of-concept
- Pressure to address limited aspects
- Pressure to conduct non-clinical tests too early
  - Product / process not defined
  - Sterilisation / packaging not defined
  - Inappropriate materials
- Minimum needed to do clinical trial application?
- Systems (risk management, design control) not achievable by all academic groups

Understanding / expertise

- Expertise in QMS, biological safety testing, CER preparation, regulatory …
- Early input expensive – but consequences of incorrect strategy / decisions can be severe
- Classification drives
  - Route to market
    - Studies needed
    - How to get into clinical trials
    - Regulatory and other bodies
  - Commercial partner interest / strategic fit
    - Length of time to market
    - Competition
    - Value inflection points
- Availability of experts, cost of input should be included in plans
- Early input to grant applications strongly recommended
- Major funding bodies (Innovate UK, Horizon 2020) insist on regulatory section in applications

Summary

- Incorrect classification
- Strategy based on individual grant requirements / funder expectations without understanding of regulatory obligations
- Regulatory advice too late
- Under-appreciation of other legislative frameworks

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