Regulatory Pathways for Non-Invasive Neuromodulation Devices – EU Perspective

Non-Invasive Neuromodulation of the Central Nervous System:
IOM, Washington DC,
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Presentation Overview

1. Who is involved in CE Marking?
   - EU Commission
   - Competent Authorities
   - Notified Bodies
   - Manufacturers
2. Why bother with CE Marking?
3. How do Manufacturers CE Mark Devices?
   - Is it a device?
   - What is the classification?
4. Conformity Assessment Routes
5. Technical Documentation & Essential requirements
   - Device-Drug Combination products
   - Declaration of Conformity  CE Mark Affixation

Who is involved?

Who are the Players?

- EU Commission: Situated in Brussels
  - ‘Civil Service’; Draft Directives & Regulations; Keep list of Harmonised Standards up to date
- Member States: 28 of them, represented by “Competent Authorities”
  - Transpose Directives into National Law; Enforce requirements
- Notified Bodies: Over 60, situated in nearly all the Member States
  - Designated by CA’s
  - Conduct Conformity Assessment
- Manufacturers
  - Uncountable, situated worldwide

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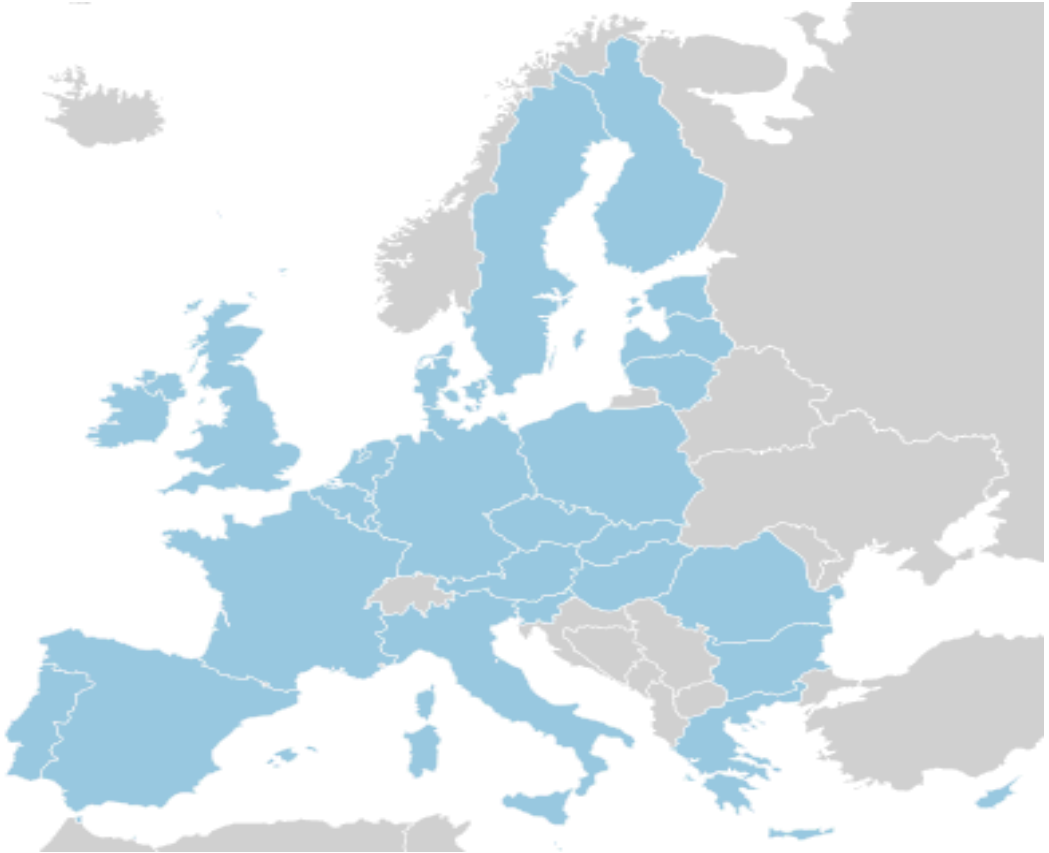
Why bother?

European Union

28 Member States
+ Norway, Iceland, Switzerland & Lichtenstein
+ Turkey

505,000,000 People
23 Official Languages

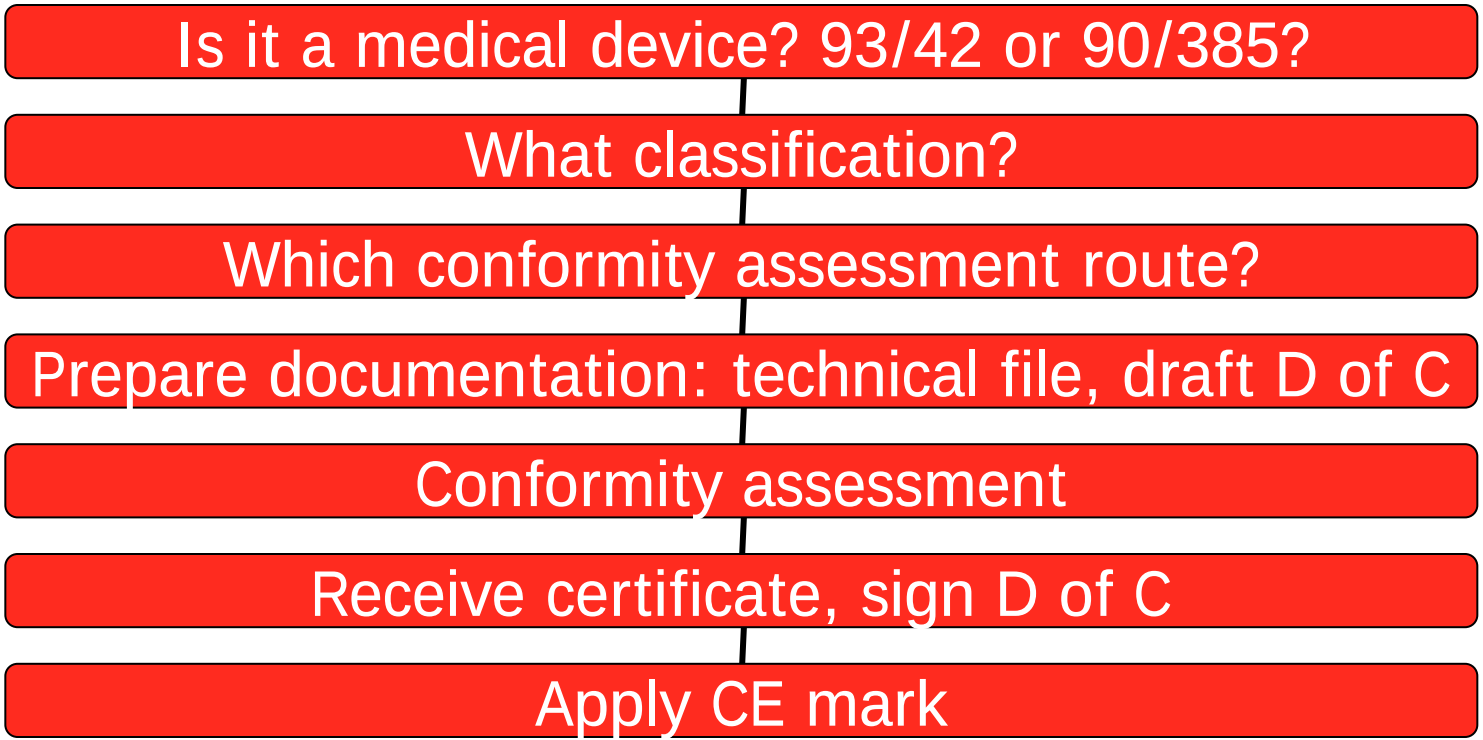
Mutual Recognition
- Australia
- Taiwan
- Saudi Arabia



Regulatory Pathways for Non-Invasive Neuromodulation Devices

93/42/EEC (MDD) and 90/385/EEC (AIMD)?

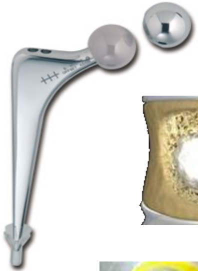
Manufacturer: Product to CE Mark



Is it a Device?

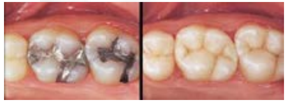
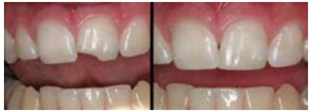
Medical Device – 93/42/EEC

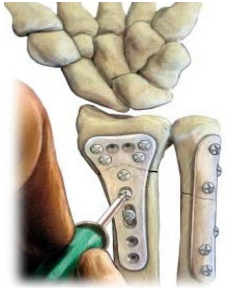


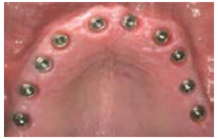


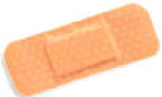


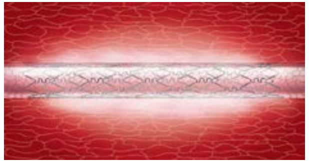









93/42/EEC

'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 injury or handicap,
- investigation, replacement or modification of anatomy or physiological process,
- control of conception,

and which does not achieve its principal intended action ... by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

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What is the Classification?

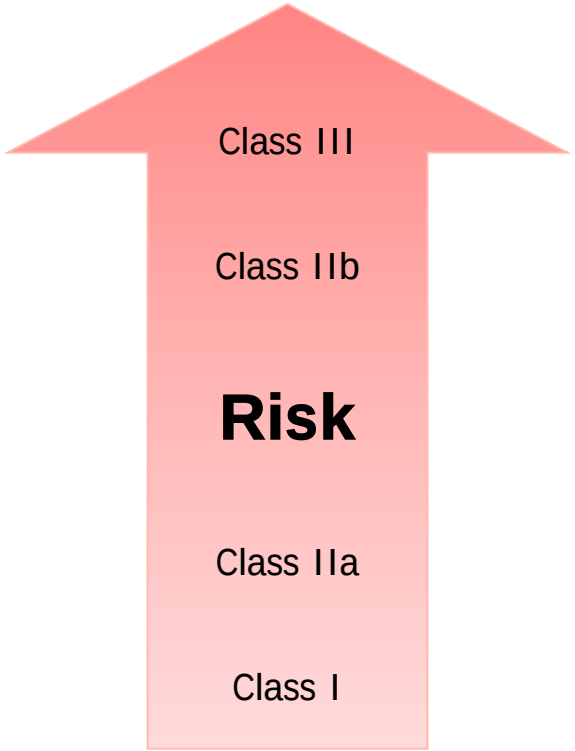
Classification – Based on Manufacturer's Intended Purpose

Device Classification:

Notified Body + Competent Authority Assessment

Notified Body Conformity Assessment

Self-Certification



Annex IX Classification Criteria

…. Para 2.1: *“Application of the classification rules shall be governed by the intended purpose of the devices”*

- Duration of contact:
  - Transient, Short term, Long term
- Degree of invasiveness:
  - Implantable, Surgical, Body orifice
- Anatomy affected
- Active / Non-active

Duration of Contact

- Transient: <60 minutes
- Short term: ≤30 days
- Long term: >30 days

  - Immediate replacement by similar device is a continuation of original use

Degree of Invasiveness

- Invasive
  - Penetrates inside the body via a body orifice or through the surface
- Body orifice
  - Natural opening or permanent artificial opening, eg stoma
- Surgical
  - Penetrating the surface in the context of surgical intervention

Annex IX Definitions

- Reusable
- Active
- Implantable

- Central Circulatory and Nervous Systems
  - 2007/47/EC increases scope of CCS

18 Classification Rules

1 - 4	Non invasive devices
5 - 8	Invasive devices
9 - 12	Active devices
13 - 18	Special rules

How to Classify

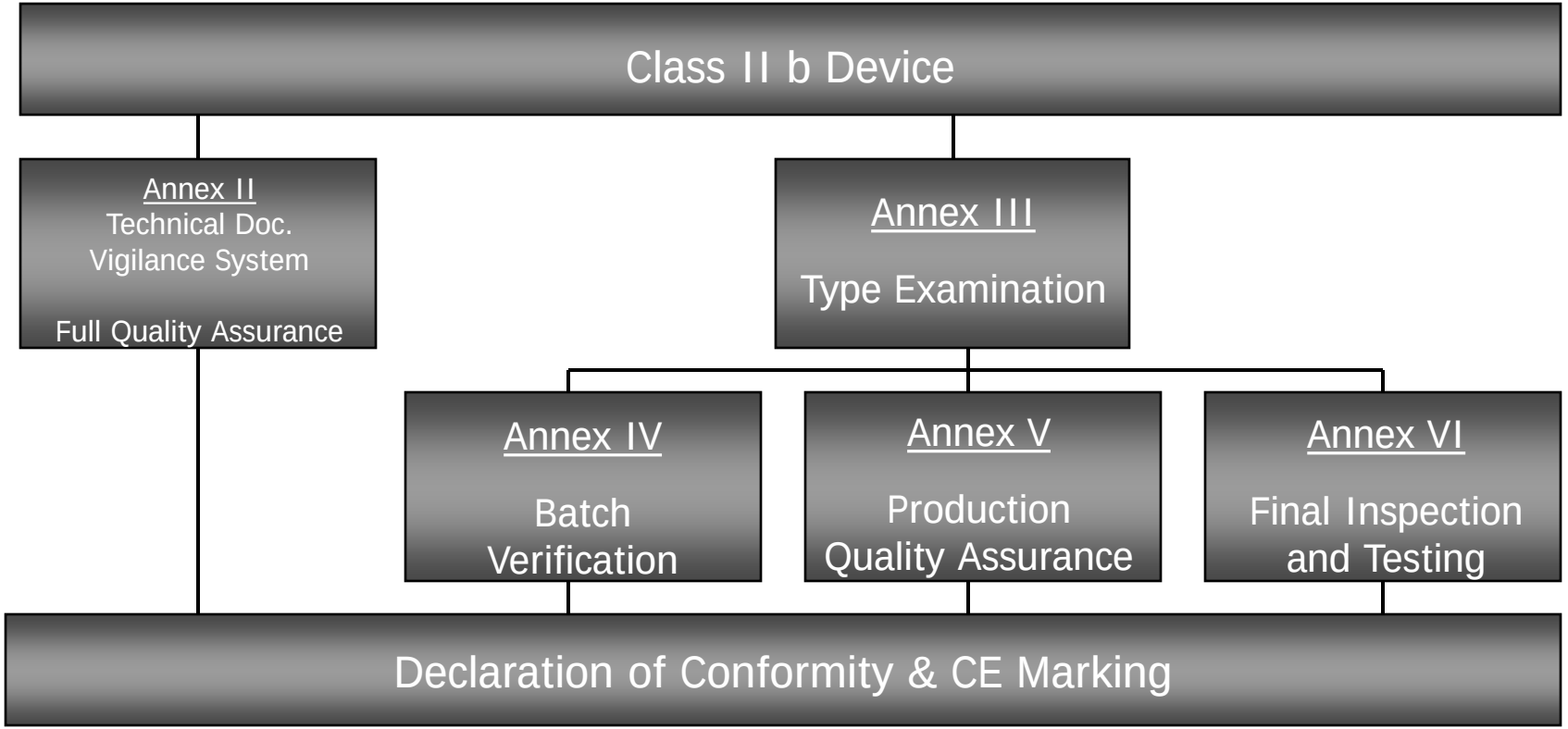
1. Intended purpose
2. Confirm it is a medical device
3. Consider the definitions
4. Consider the implementing rules
5. Decide on the applicable rule
6. Classify

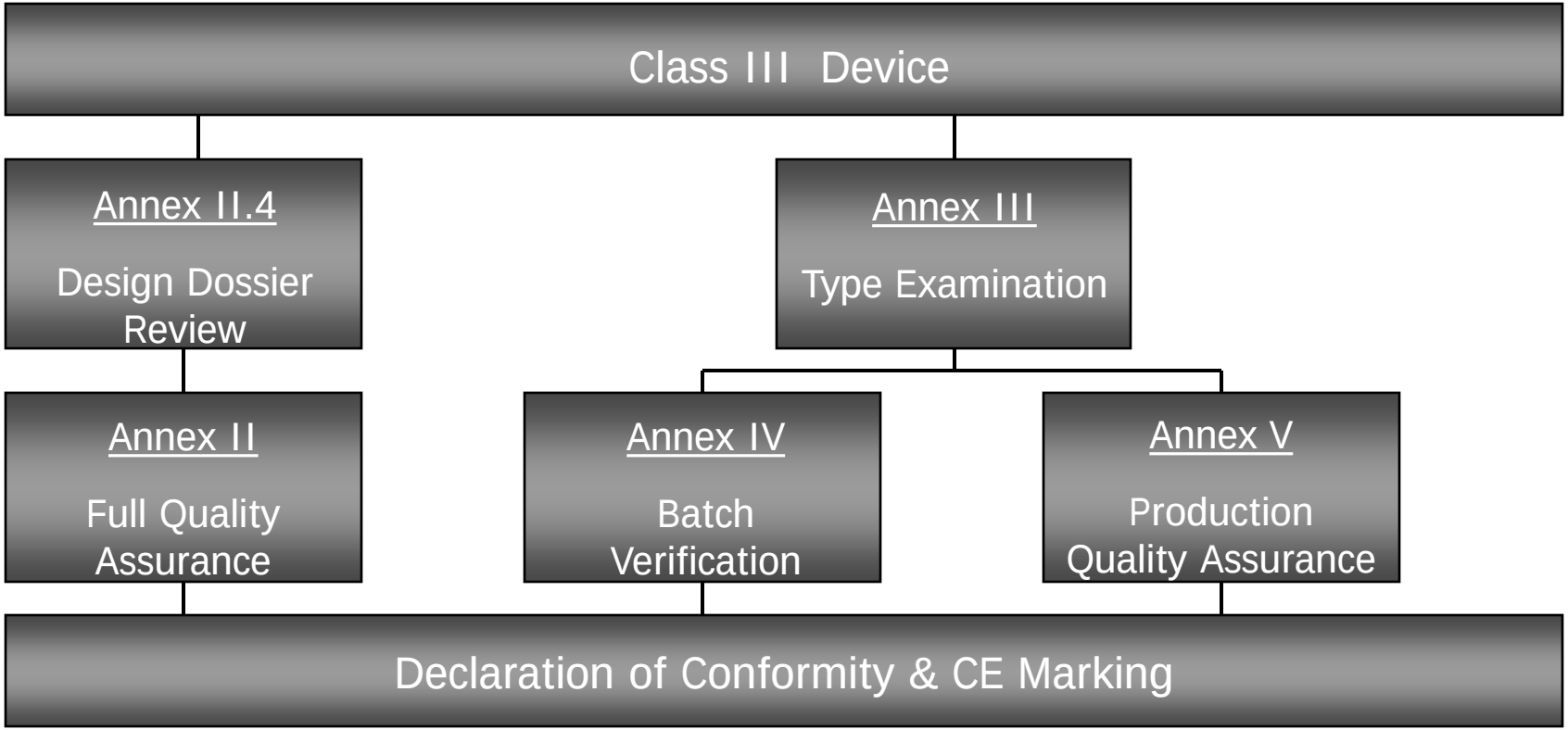
Conformity Assessment

Conformity Assessment Annexes

Product Annexes	
Annex II **Para 4**	Design Examination
Annex III	Type Test
Annex IV	Batch Release

Quality System Annexes	
Annex II **Para 1-3, 5-8**	Design, Manufacture and Final Inspection
Annex V	Manufacture and Final Inspection
Annex VI	Final Inspection and Testing





Technical Documentation & Essential Requirements

93/42/EEC – Annex VII

The technical documentation must allow assessment of the conformity of the product with the requirements of the Directive. **It must include in particular:**

- general description of the product and intended use(s),
- design drawings, methods of manufacture, diagrams of components,
- explanations necessary to understand the operations of the product,
- results of the risk analysis,
- list of harmonised standards, applied in full or in part,
- descriptions of the solutions adopted to meet the ERs,
- in the case sterile products validation report,

93/42/EEC – Annex VII

and ... :

- results of the design calculations and inspections carried out,
- if the device is to be connected to other device(s), proof must be provided that it conforms to the ERs,
- solutions adopted as referred to in Annex I,
- pre-clinical evaluation,
- clinical evaluation in accordance with Annex X,
- label and instructions for use.

General Essential Requirements 1- 6: Summary

1. Safe - benefits outweigh risk
2. State of the art - inform of residual risks
3. Perform as intended
4. Lifetime defined
5. Packaging suitable for transport and storage
6. Side effects acceptable

6a. Clinical data

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Notified Bodies Assessment: Device-Drug Combination

Key Essential Requirements:

- ER 1
  - Devices must not compromise the clinical condition of patients
  - Risks are acceptable when weighed against the benefits to the patient
- ER 7.4
  - Verification of safety, quality and usefulness of the substance ... by analogy with .... Directive 2001/83/EC
  - NB must consult a Drug CA before taking its decision
  - NB shall only consult drug CA having verified the usefulness of the substance taking into account the intended purpose of the device
  - NB will give due consideration to the views of the Drug CA when making its decision
  - **NB will almost certainly not go against a negative Drug CA opinion**

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Notified Bodies Assessment: Device-Drug Combination

- Review Process Overview:
- **Device Aspects**:
  - Reviewed by NB per requirements in appropriate Directive
- **Medicinal Aspects**:
  - NB conducts initial review of **USEFULNESSS** of medicinal substance.
  - Above usefulness report together with Medicinal Data package is reviewed by Medicinal CA/EMA
  - Medicinal CA/EMA review focus is on**: QUALITY** and **CLINICAL SAFEFTY** of the Medicinal substance.
  - Medicinal CA/EMA provides final review report to NB who makes a Certification decision.

Available Guidance on Classification

- Speak to NBs with experience of Device Drug Combinations
- MEDDEV 2.1/3 Rev 3
- MHRA Bulletin No. 17 – Medical devices and Medicinal Products
- MHRA Guidance Note No 8 – A Guide to what is a Medicinal Product
- Manual on borderline and Classification in the Community Regulatory Framework for medical devices

  http://ec.europa.eu/health/medical-devices/documents/borderline/index_en.htm

Notified Bodies Assessment: Device-Drug Combination

Considerations for device-drug combinations:

- Properties of medicinal substance considered in manufacturing controls, processing parameters and storage conditions
- Appropriate controls on the medicinal substance to assure quality in the device is maintained
- Stability should be conducted in accordance with ICH
- Quality Management System considers the importance of the medicinal substance as well as the device aspects
- Controls taken to minimise risk of harm to end user
- Use relevant guidance documents from EMA where relevant

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&mid=WC0b01ac05800240cb

- Dossier in line with MEDDEV 2.1.3 or CTD format

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Notified Bodies Assessment: Device-Drug Combination

Certification and CE-mark:

CA/EMA provide a scientific opinion report to NB

- **Positive Outcome**: NB issues EC Design Exam Cert and informs CA/EMA of its decision. Manufacturer prepares Declaration of Conformity and applies CE Mark

- **Negative Outcome**: The NB may not issue the Certificate

ERs – Summary

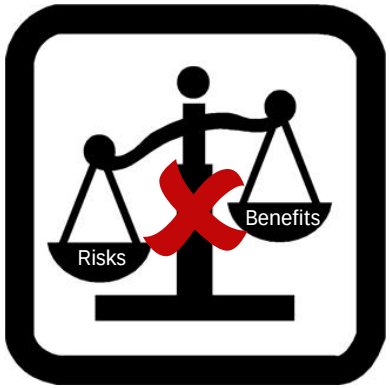
- Devices must be safe and fit for their intended purpose
- Manufacturers must demonstrate the Essential Requirements have been addressed and where appropriate met before applying CE mark
- Evidence of compliance shall be included or referenced in the manufacturers technical documentation
- Clinical data must be properly established and must be kept up to date
- May use standards to demonstrate conformity (preferably harmonized)

Risk Management

Per EN 14971:2012

Essential Requirement #6

"Benefits > Risks"



Declaration of Conformity

DOC NB-Med Consensus Statement:

Title of the document	Declaration of Conformity
Identification of the legal entity	Name and address of the manufacturer (and authorised representative)
Identification of the device(s)	Name, type or model
Identification of products where required for the selected conformity assessment procedure.	The DoC may cover particular lots, batches, serial numbers, particular products types and/or particular periods of manufacture.
A statement that the identified devices meet the applicable provisions of the Directive.	'We hereby declare that the above mentioned devices comply with the legislation of the UK transposing European Medical Devices Directive 93/42/EEC'
Date of validity	Date from which the DoC is valid
Identification of the person authorised to sign.	Name, position and signature of the person, who is approving the DoC

Conclusions

- Medical Device: Definition & Scope of the MDD (or AIMD?) .
- Classification – consider ALL applicable Rules.
- Conformity Assessment
- Compliance with ALL applicable Essential Requirements
  - Clinical Data (Clinical Equivalence)
  - Risk Management
  - Labeling
- Device-Drug Combinations, MUST consult with a CA
- Affix CE Mark ……and Place on the Market

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Any Questions…..and Contact Us

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