NSAI and Enterprise Ireland: Briefing on Medical Device Regulation and Brexit

25th & 27th February 2019
Galway & Dublin

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ENTERPRISE IRELAND
where innovation means business

GETTING IRELAND BREXIT READY

Agenda

- Introduction and overview (Dr Caroline Dore-Geraghty)
- Implications of Medical Device Regulation and Brexit on MedTech Industry: A Notified Body perspective (Colm O'Rourke)
- Device classification and product technical file requirements for the Medical Device Regulation (Aishling Owens & Susan Murphy)
- Medical device regulation and quality system requirements (Niamh Lynch & Tom Patten)
- Clinical requirements for the Medical Device Regulation (Yvonne Ndefo)
- Overview of Enterprise Ireland Brexit Supports for SMEs (Manus Rooney & Jonathan McMillan)
- Wrap up and Q&As

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Implications of MDR and Brexit on MedTech Industry

NSAI & Enterprise Ireland Briefing on
MDR and Brexit, February 2019

Colm O'Rourke
Business Development

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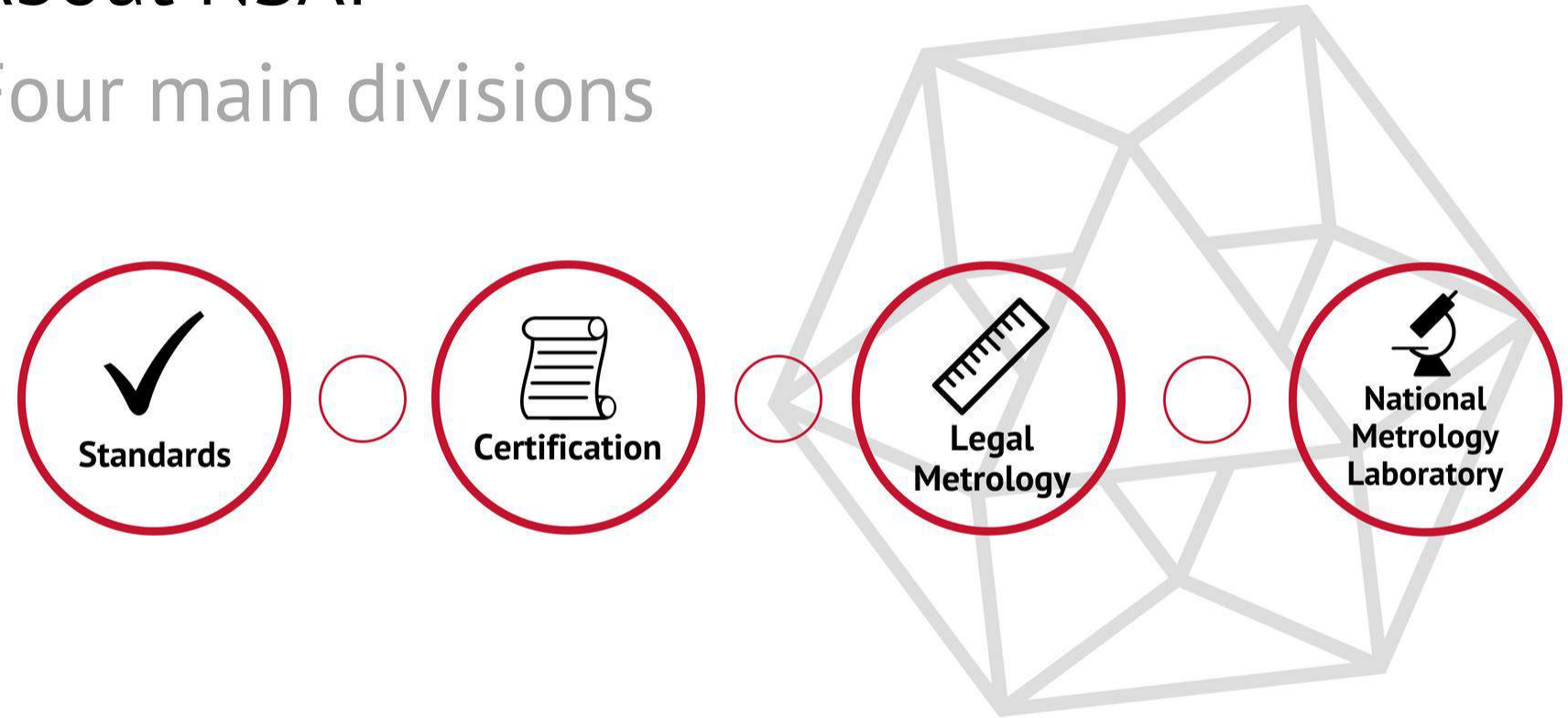
About NSAI

Four main divisions



What I will discuss

- Current status
- Practical implications & regulatory strategy
- Brexit
- Closing

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Current Status

- Timelines
  - Entry into force: 27th May 2017
  - Date of application: 27th May 2020
  - MDD certificates potentially valid until 27th May 2024
- Requirement regarding PMS, vigilance and registration of economic operators apply from date of application
- General MDR preparation is well underway in industry
  - NSAI is encouraging open communication regarding transition plans between manufacturers and the Notified Body

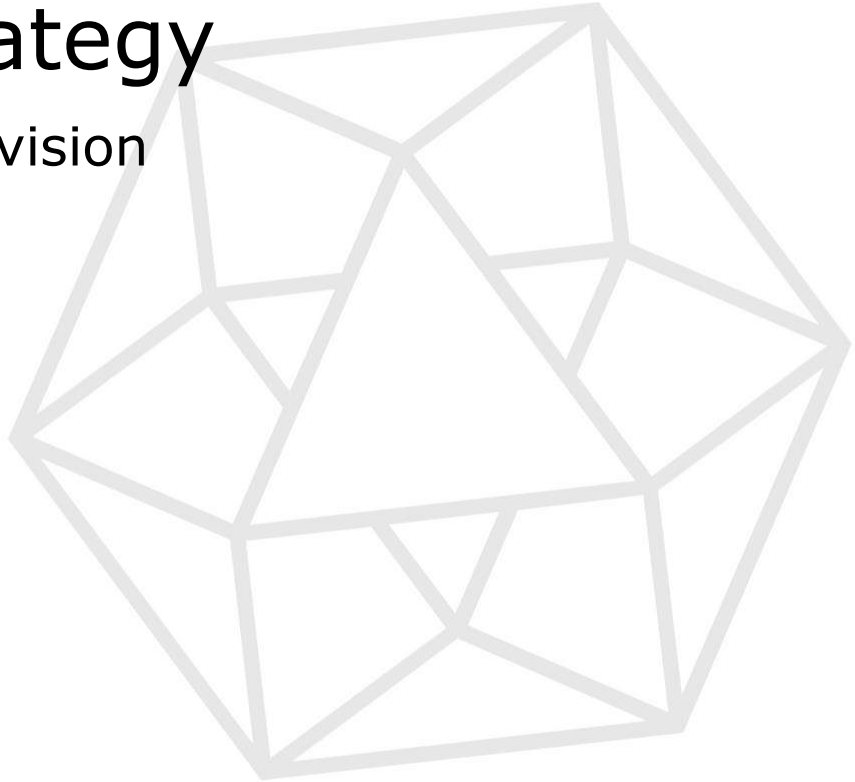
Current Status

- Notified Body Designation
  - 1 NB designated against MDR (BSI UK)
  - ~30 application in process according to a Team-NB survey
  - Lengthy and time consuming process
- Many manufacturers are recertifying their existing devices under the MDD in order to delay full MDR transition
  - This is resulting in increased workload for both industry and NB's
- Guidance documents and Common Specifications being generated to support interpretation

Practical Implications & Regulatory Strategy

- Technical documentation revision
  - GSPR
  - PMS
  - Risk analysis
  - Labelling

- Additional testing
  - Hazardous substances
  - Biocompatibility
  - Clinical investigations



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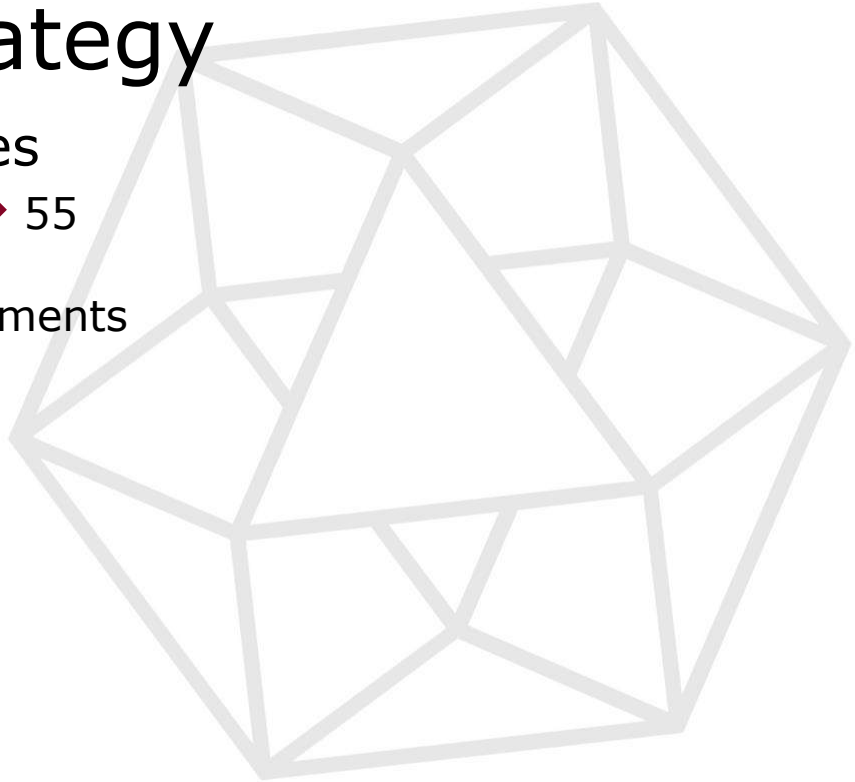
Practical Implications & Regulatory Strategy

- Time
  - Earlier engagement with Notified Bodies
  - Potentially longer time to market
  - Staffing – increased ongoing interaction with Notified Body
- Cost
  - Increased review times = increased cost
  - Increased testing/clinical data
  - Staffing

Practical Implications & Regulatory Strategy

- Notified Body capacity issues
  - Decreasing numbers: 83 → 55
  - Increased competency requirements
  - Longer lead-times
  - Increased workload



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Practical Implications & Regulatory Strategy

- MDR adoption – early vs late

Early:

  - Element of unknown
  - Possibly tidier in terms documentation – all under one system
  - Companies in early development – MDR offers clearer rules

Late:

  - More time to prepare – testing/clinical/documentation
  - Availability of guidance documents and CS
  - Can not make any significant change to design or intended use after date of application
  - Some MDR requirements will be applicable to these products as of date of application: PMS etc.
  - NB capacity to recertify device ahead of May 2020

Practical Implications & Regulatory Strategy

- Longer term approach needed
  - Extended approval times considered at product development stage
  - Significant changes planed further in advance
- Portfolio review
  - Will all products be sustainable into the future
  - Revenue versus cost of keeping on the market
- Review of markets which rely on CE
  - Use of 510K for TGA approval
- Cooperation between RA and strategic business planning
  - The business strategy and RA strategy must align
  - RA requirements should inform the business strategy

Brexit

- Brexit
- +
- MedTech
- =

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Brexit

- Status of UK Notified Bodies
  - In no-deal scenario UK based NB's will lose their status
  - Products which they have certified pre 29th March and which have been "placed on the market" can continue to be made available (date of placing on the market is the date of the transaction between the manufacturer and the EU 27 customer. Placing on the market does not require physical delivery of the product)
  - Products produced after 29th March which are destined to be placed on the EU market must be assessed by an EU 27 NB – i.e. EC certificate covering that product must be with an EU 27 NB

Brexit

- Status of UK Notified Bodies continued
  - Where a manufacturer has transferred from UK NB to EU 27 NB, products produced after the transfer must bear the NB number of new NB
  - DOC and Notified Body Certificate will be updated – consider knock on effect on certificates of free sale, registrations in countries which rely on CE mark

Brexit

- Implications for product leaving the UK
  - UK will be considered a third country – customs & tariffs
  - UK based manufacturers will need an EU 27 based Authorised Rep
  - The entity which brings product into an EU 27 country from the UK will become an importer*
  - What is the certification status of the product being imported from the UK

*See MDR Article 13 for obligation of importers

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Brexit

- Implications for product entering the UK
  - MHRA will accept the CE mark for a time-limited period
  - Non UK manufacturers will require a UK based "Responsible Person"
  - This "Responsible Person" is not required on the labelling
  - Devices must be registered with MHRA – for non-UK manufacturers this will be done by your UK Responsible Person
    - Grace period for this registration:
      - Class III, IIb implantable, AIMD and IVD List A: 4 months
      - Class IIb non-implantable, IIa, IVD List B and Self-test IVD: 8 months
      - Class I medical devices, Self-certified IVD's and Class A IVD's: 12 months

Closing

- We are all facing significant challenges
- Cooperation and communication will be key
- Engage early and often – with you Notified Body

Thank you.

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MDR Technical Documentation Requirements

Susan Murphy
European Medical Device Operations Manager Dublin

Aishling Owens
Certification & Inspection officer Galway

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Technical Documentation

European Commission

Medical Devices Regulation

EU MDR

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Requirements

- **Section 1.0 (Annex II)**
  - Device description and specification including variants and accessories
  - Reference to previous generations of the device
- **Section 2.0 (Annex II)**
  - Information to be supplied by the manufacturer
- **Section3.0 (Annex II)**
  - Design and Manufacturing information
- **Section 4. (Annex II)**
  - General safety and performance requirements
- **Section 5. (Annex II)**
  - Benefit risk analysis and risk management

Requirements Continued

- **Section 6 (Annex II)**
  - Product Verification and Validation
    - Pre clinical and clinical data
    - Additional information required in specific cases
- **Section 7 (Annex III)**
  - The Post Market Surveillance Plan
  - The PSUR
- **Additional information required in specific cases**
  - Drug device combinations
  - Human blood/plasma
  - Human/Animal tissue
  - Substances that are absorbed or dispersed in the body
  - Class III and Class IIb active devices intended to administer or remove a medicinal product from the body **(Rule 12)**

What you need to know

Know the Players!!!

- The manufacturer's role;
  - **Art 10**
  - **Annex I GSPR**
  - **Art 61 & Annex XIV (clinical evaluation)**
  - **Annex II & III (technical documentation)**
  - **Art 19 & 20 (doc & CE Marking)**
  - **Art 27, 29 & 31 (UDI)**
  - **Art 83 (PMS)**
  - **Art 87 &88 (Vigilance)**
  - **Art 30(1) (outsourced processes)**
- What the Notified Body looks for **Annex IX**
- What the Competent Authority looks for **Art 45, Annex VII**

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Developing technical documentation

- Conformity assessment procedure**, Art 52**
- Classify your device, **ART 51, Annex VIII**
- Choose your route of conformity
- Differentiate between Class IIb and Class IIb implantable **Art 52 paragraph 4**

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Device description and specification Section 1.0 Annex II

1

- Product or trade name + a general description
- Rationalisation that the product is an actual medical device **Art 2** (definition of a medical devices)
- Basic UDI, **ART 27,28 Annex VI**
- Intended patient population and medical condition to be treated/diagnosed/monitored
  - Patient selection
  - Indications
  - Warnings/contra-indications
- Principles of operation
- Device classification **Annex VIII**
- Explanation on any Novel features
- Details of various configurations that will be made available

Device description and specification Section 1.0 Annex II

- Description of the key functional elements
- Description of the raw materials incorporated into the functional elements
  - Particularly those having direct or indirect contact
- Technical specifications
- An overview of previous generations of the device
- An overview of similar devices

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Information to be supplied by the Manufacturer Section II, Annex II

2

- Complete set of labelling at all levels
- Copy of the IFU
  - In the language of the member state where the device is for sale

EN 1041:2008

Information supplied by the manufacturer of medical devices

EN ISO 15223-1:2016 - replaced EN980:2008

Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements (ISO 15223-1:2016, Corrected version 2017-03)

Design and Manufacturing Information Section III Annex II

3

Description of each design stage

- Information and specifications on
  - Manufacturing processes and their validations
  - Continuous monitoring
  - Final testing
- Identification of all sites including suppliers and sub-contractors
  - Design
  - Manufacturing
  - Assembly
  - sterilisation

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General Safety and Performance Requirements Section IV Annex II

4

- Shall be applicable to the device and include
  - Justification, validation and verification of the solutions adopted
- Explanation where GSPR do not apply to the device
- Method to demonstrate compliance to the GSPR
- Details of the HS/CS applied
- Identity of the document demonstrating conformity with the HS/CS to the GSPR
  - Traceable to the location of such evidence within the full Technical documentation

Benefit and Risk Management Section V Annex II

5

- The documentation shall contain information on
  - They shall be designed and manufactured to be safe and effective taking account of the generally acknowledged state of the art **Annex 1 Chapter 1 Section 1**
  - All known and foreseeable risks shall be minimised when weighed against the benefits to the patient **Annex 1 Chapter 1 Section 8**
  - Solutions adopted and the results of the risk management **Annex 1 Chapter 1 Section 3**
- **Risk management shall be understood to be a continuous process**

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Product verification and validation Section VI, Annex II

6

- Results and critical analysis of all verification and validation tests

Verification

Validation

Pre-clinical and clinical data Section VI.1 , Annex II

- Test results
  - Engineering
  - Laboratory
  - Simulated
  - Animal
  - Evaluation of published literature **applicable to the device**
- Detailed information on
  - Test design
  - Complete test or study protocols
  - Method of data analysis
  - Biocompatibility
  - Physical, chemical and microbiology characteristics
  - Electrical safety and EMC
  - Software verification and validation
    - As used in the finished device

Pre-clinical and clinical data Section VI.1 Annex II

- Stability
- Performance and safety
- Where no new testing has been carried out a **rational shall be provided**
- The clinical evaluation plan report and updates **Art 61(12) & Annex XIV**
- The PMCF plan and report **Part B Annex XIV** or a justification why it is not applicable

Technical Documentation Annex III
Post Market Surveillance

- The PMS must be
  - In accordance with **Art 83-86**
  - Clear
  - Organised
  - Searchable
  - Unambiguous

- PMS system of the manufacturer **Art 83**
- Post market surveillance plan **Art 84**
- Post Market surveillance report **Art 85**
- Periodic safety update report **PSUR Art 86**
  - Class IIb & Class III Annually, upload electronically **Art 92**
  - **This will be reviewed and commented upon by the NB Art 92**
  - Class IIa every 2 years, required to be available to the NB & CA

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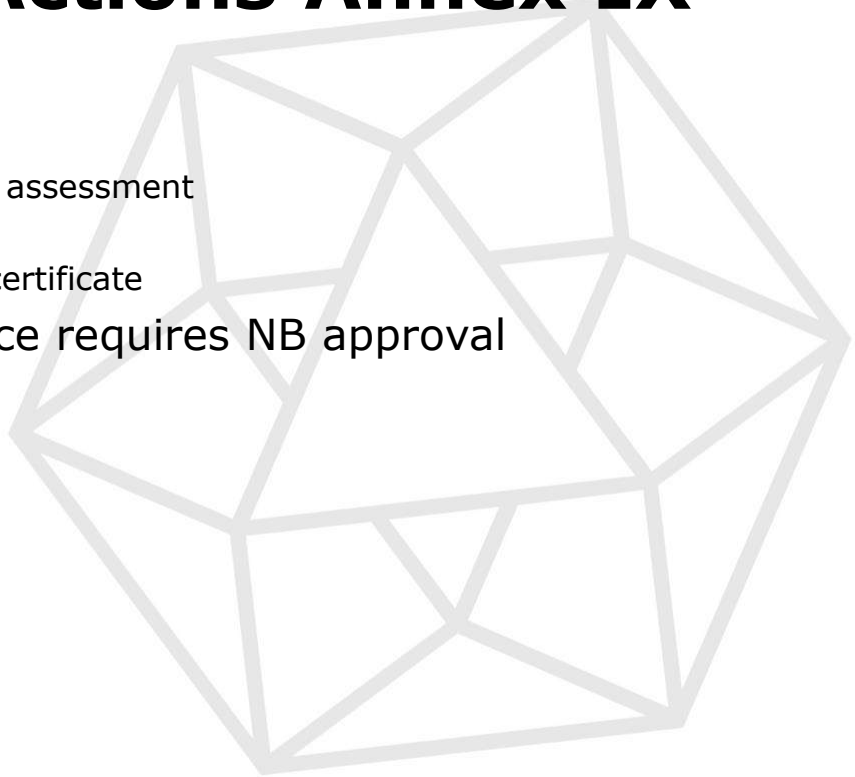
Notified Body Actions Annex IX

- Examine the application
  - May require additional tests
- Examine the clinical evidence
  - Examine any claims of equivalence and assess the suitability of using such data taking into account factors such as new instructions or innovations
- Verify that the clinical evidence and clinical evaluation are adequate
- Verify the conclusions drawn by the manufacturer
  - Conformity with the GSPR
  - Adequacy of the risk benefit analysis and conclusion
  - IFU
  - User training
  - PMS Plan
  - PMCF plan proposed where applicable

Notified Body Actions Annex IX

- Provide the manufacturer with
  - A report on the technical documentation assessment
  - A clinical evaluation assessment report
  - A Technical documentation assessment certificate
- Any changes to the approved device requires NB approval



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Additional requirements in specific cases Section VI.2 Annex II

Class III & Class IIb

Devices containing medicinal product or a medicinal product derived from Human Blood or Plasma

- **Manufacturer's responsibilities**
- The manufacturer shall
  - A statement declaring the above
  - The source of the substance
  - The tests conducted to assess the
    - Safety
    - Quality
    - Usefulness
  - Taking account o the intended purpose of the device
  - Report any changes to the manufacturing process of the substance to the NB
  - Shall inform the NB of the release of the batch of devices containing human blood or plasma together with the official certificate concerning the release of the batch of human blood or plasma derivative used in the device
  - Issued by designated laboratory

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Devices containing medicinal product or a medicinal product derived from Human Blood or Plasma

- **Notified Body responsibilities**
- The NB shall
  - Verify the usefulness of the substance
  - Seek a scientific opinion from
    - a CA or EMA for a drug
    - EMA for Human Blood or Plasma
  - The opinion shall be provided within 210 days of receipt
  - In the case of a change
  - Consult with the medicines authority to ensure the quality and safety of the substance is unaffected
  - An opinion will be provided in 60 days
  - When the medicines agency is notified of information on the ancillary substance that could impace on the risk or benefit they will contact the NB for action

Devices manufactured utilising tissue or cells of Human or Animal origin

- **Manufacturer's responsibilities**

- The manufacturer shall
  - Identify all material of Human or Animal origin
  - Provide detailed information concerning conformity with ER 13.1 & 13.2 respectively

Devices manufactured utilising tissue or cells of Human or Animal origin

- **Notified Body Responsibilities**
- The NB shall (Human tissue or cells)
  - Seek an opinion from one of the CA's on the donation, procurement and testing of the tissues or cells of human origin or their derivatives
  - Submit s summary of the preliminary assessment which provides information on
    - Information on the non-viability of the human tissue or cells in question
    - Donation, procurement and testing
    - Risk benefit of the incorporation o the tissues into the device
  - The CA shall provide its opinion to the NB within 120 days of receipt of all data
  - The NB shall consider the CA opinion in its overall decision
    - **If the decision of the CA is unfavourable The NB cannot certify the device**
  - All changes particularly to the donation, procurement or testing shall be reported to the NB
  - The report will be transmitted to the same CA who approved the original
  - The CA will report to the NB within 60 days
    - **If the decision of the CA is unfavourable The NB cannot certify the device**

Devices manufactured utilising tissue or cells of Human or Animal origin

- **Notified Body Responsibilities**
- The NB shall (Animal tissue)

- Follow the requirements laid out in EU 722/2012 (No Change)

Devices containing substances that are absorbed or dispersed into the Human Body

- **Manufacturer's responsibilities**
- The manufacturer shall
- Provide detailed information including
  - Test design, Complete test or study protocols, Methods of data analysis, data summaries and test conclusions in relation to
  - Absorption, distribution, metabolism & excretion
  - Possible interaction of those substances or their products of metabolism in the human body with other devices or medicinal products
  - Local tolerance
  - Toxicity including single dose toxicity, repeat dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity depending on the level and nature of exposure to the device
  - In the absence of such studies a justification shall be provided

Devices containing substances that are absorbed or dispersed into the Human Body

- **Notified Bodies responsibilities**
- The NB Shall assess the
  - Quality and safety of the devices for the evaluation of absorption, distribution, metabolism, excretion, local tolerance, toxicity, interaction with other devices , medicinal products or other substances and potential adverse reactions
  - Seek an opinion form a duly designated CA or EMA on the compliance of the device with the relevant requirements laid sown in Annex I to Directive 2001/83/EC
  - The opinion shall be drawn up within 150 days from receipt
  - Give due consideration to the opinion received in its final decision

Devices containing CMR or Endocrine disrupting substances

- **Manufacturer's responsibilities ER 10.4.1**
- The manufacturer shall provide a justification based on
  - An analysis of potential patient or user exposure
  - An analysis of potential alternative substances, materials or designs
  - A justification as to why possible substance or material substitutes, if available, or design changes are inappropriate in maintaining the functionality performance, risk-benefit ratios o the product taking into account if the intended use of such devices includes children and pregnant women
- **Notified Body Responsibilities**
  - The NB shall review the arguments provided by the manufacturer whether or not the arguments presented are valid, and determine the device is safe for its intended purpose

Class III implantable and Class IIb to administer and or remove a medicinal product (Rule 12)

- **Manufacturer's responsibilities**
- The manufacturer shall provide the clinical revaluation report **Art 61(12) & Section IV Annex XIV**
- The report shall support the assessment of the conformity of the device.
- It shall include clinical and non-clinical data allowing the manufacturer to demonstrate conformity with the **GSPR**
- Both favourable and non-favourable data considered shall be included

Class III implantable and Class IIb to administer and or remove a medicinal product (Rule 12)

- **Notified Body responsibilities**
- The NB shall:
  - Develop a Clinical Evaluation Assessment Report (**CEAR**) detailing it's conclusions on the manufacturer's clinical evidence provided specifically regarding
    - the risk-benefit determination
    - Consistency of the evidence with the intended purpose
    - The medical indication(s)
    - The PMCF Plan **(Annex XIV Part B)**
  - Transmit the CEAR to The Commission
  - The Commission shall transmit the CEAR to the relevant expert panel **(Art 106)**
  - The NB may be requested to present its conclusions to the expert panel

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Class III implantable and Class IIb to administer and or remove a medicinal product (Rule 12)

- **Expert Panel Responsibilities**
- The expert panel shall;
  - Decide under the supervision of The Commission based on the following criteria
    - The novelty of the device or its related clinical procedure and the possible major clinical or health impact
    - A significant adverse change in the benefit-risk profile due to scientifically valid health concerns of components or materials , or the impact on health in the case of device failure
    - A significantly increased rate of serious incidents in respect of a specific device category **(Art 87)**
  - **Provide a positive scientific opinion**
    - **Within 60 days** of receipt of the documentation from the Commission, based on the NB's CEAR
  - **Not to provide an opinion**
    - **Within 21 days** of receipt of the documentation from the Commission,
  - Inform The Commission **within 21 days** of it's decision to provide or not provide an opinion

Class III implantable and Class IIb to administer and or remove a medicinal product (Rule 12)

- **The Notified Body Responsibilities post decision**
- If no opinion is delivered **within 60 days,** the NB may proceed with the certification procedure
- Approve the device based on a positive opinion
- In the case of a negative opinion the NB may advise the manufacturer to;
  - Restrict the intended purpose to certain groups of patients or certain medical indications
  - Impose a limit on the certificate validity to allow the manufacturer to undertake certain PMCF studies
  - Adapt the IFU or the summary of safety and performance to impose other restrictions
  - Provide justification to the Commission on its decision. This justification together with the opinion will be uploaded to EUDAMED by The Commission
- Guisance for expert panels for consistent interpretation prior to DOA

Thank you.

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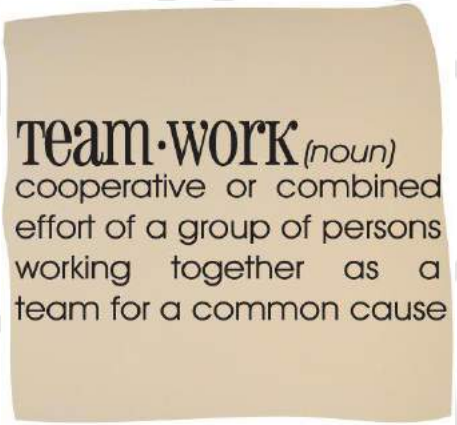

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MDR and Quality System Requirements

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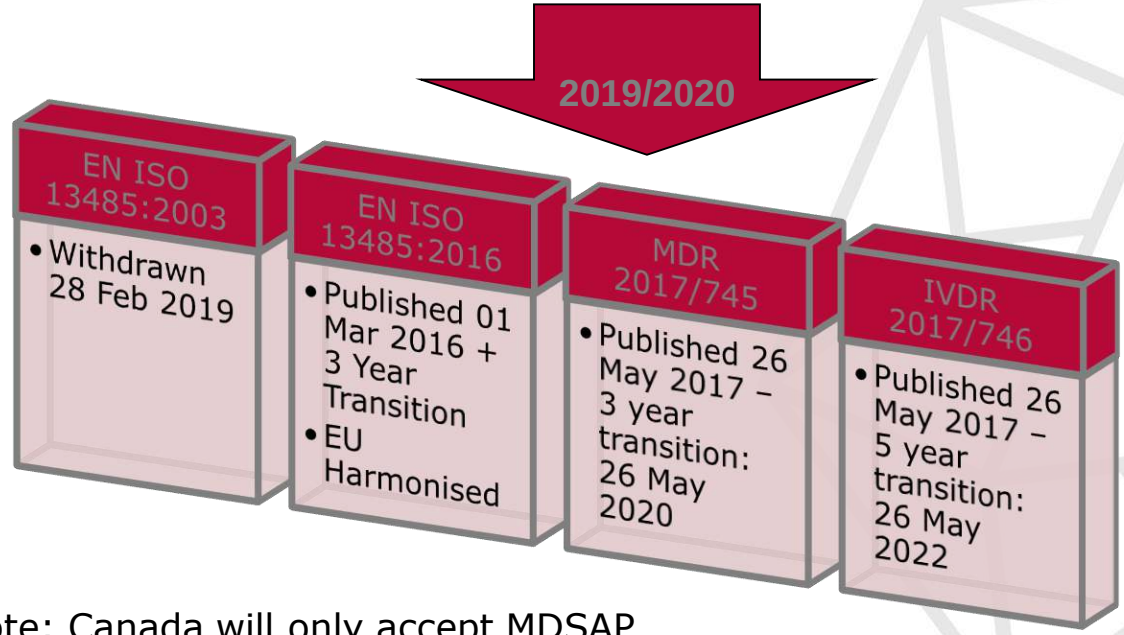
Timelines



Note: Canada will only accept MDSAP Certificates from January 2019 (extended to April 2019).

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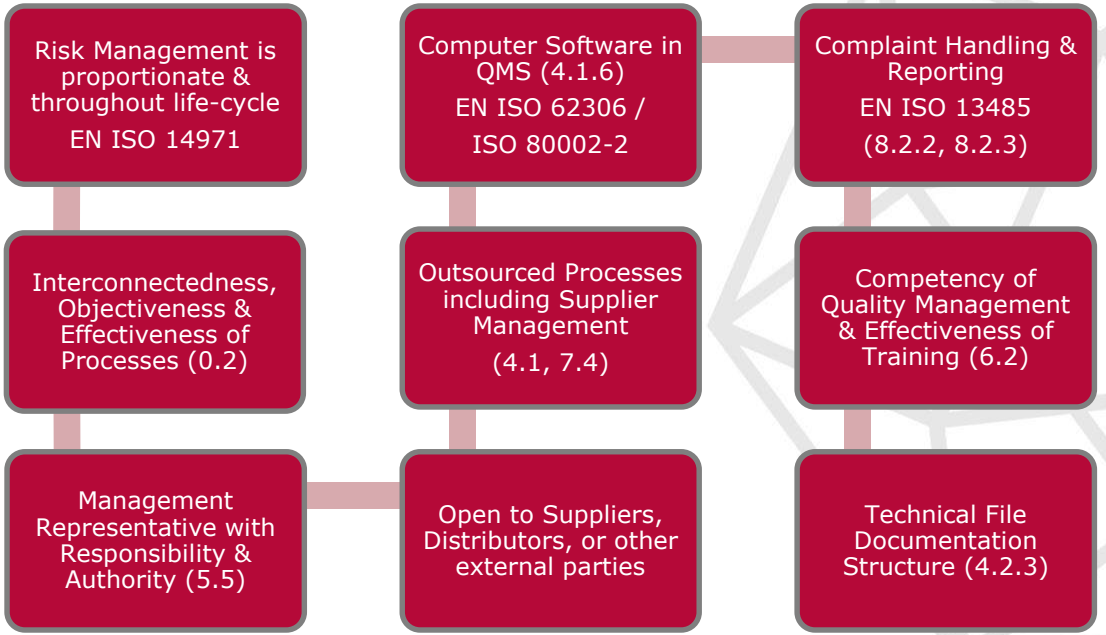
Key Changes under 13485:2016



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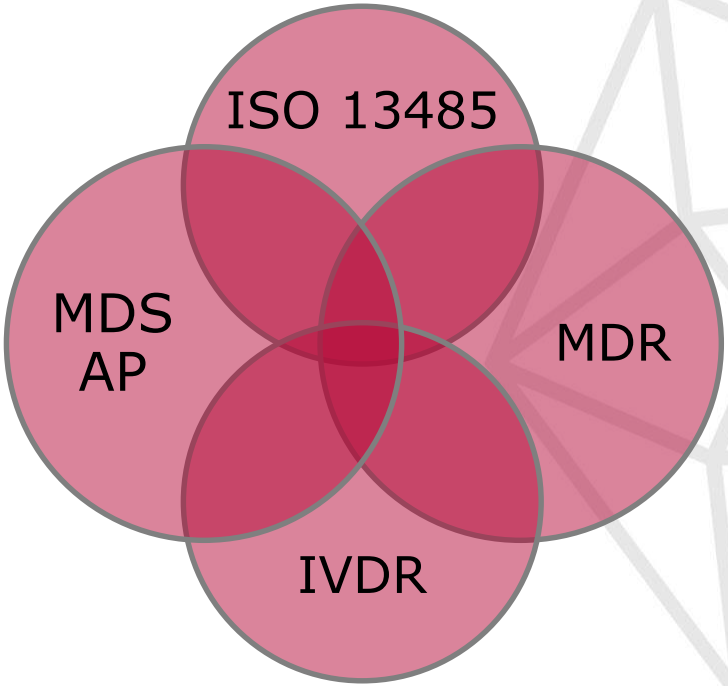
Risk-based approach



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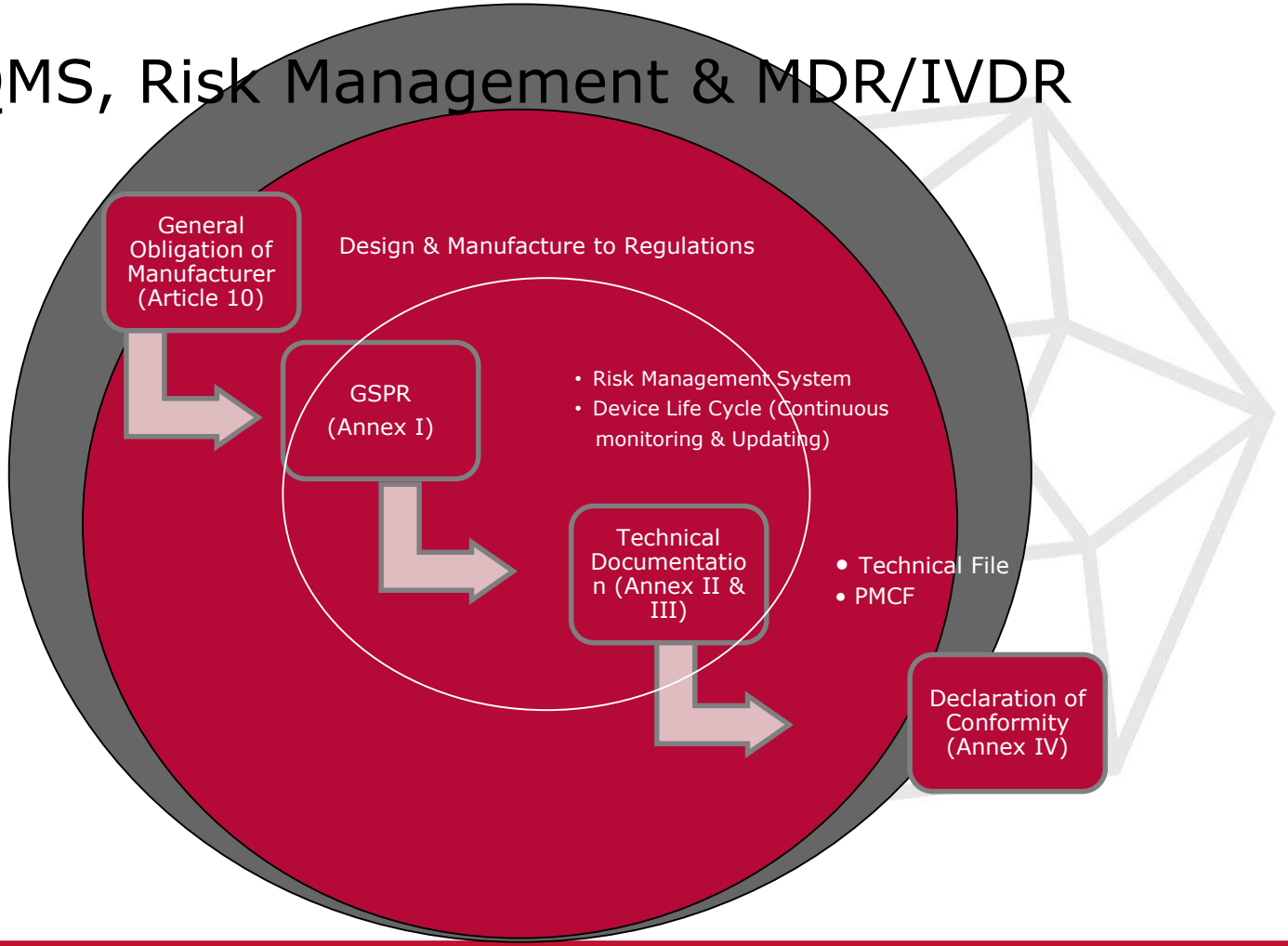
QMS, Risk Management & MDR/IVDR



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How well integrated is your risk management system?

- Classification of Device based on Risk
- Complaints Handling; Post-Market Surveillance
- Supplier Management; Incoming Inspection through continuous evaluation
- General Safety & Performance Requirements Vs. Essential Requirements (GSPR/ER)
- Clinical Evaluation & CER MEDDEV 2.7.1 Rev. 4
- Labelling standards changes
- Full Product Life-Cycle, Concept through Decommission
- Software / Electrical Medical Equipment

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MDR Article 10, section 9 QMS Requirements	ISO 13485:2016 Reference	Internal Document Reference
(a) A strategy for regulatory compliance, including compliance with conformity assessment procedures and procedures for management of modifications to the devices covered by the system;	4.11, 7.3.9	
(b) identification of applicable general safety and performance requirements and exploration of options to address those requirements;	7.2.1c), 7.3.3	
(c) responsibility of the management;	5	
(d) resource management, including selection and control of suppliers and sub-contractors;	6, 7.4.1	
(e) risk management as set out in in Section 3 of Annex I;	4.1.2, 7.1	
(f) clinical evaluation in accordance with Article 61 and Annex XIV, including PMCF	7.3.7	
(g) product realisation, including planning, design, development, production and service provision;	7.1, 7.3.2, 7.3.8, 7.5.1	
(h) verification of the UDI assignments made in accordance with Article 27(3) to all relevant devices and ensuring consistency and validity of information provided in accordance with Article 29;	7.5.8	
(i) setting-up, implementation and maintenance of a post-market surveillance system, in accordance with Article 83;	8.2.1, 8.5.1	
(j) handling communication with competent authorities, notified bodies, other economic operators, customers and/or other stakeholders;	7.2.3	
(k) processes for reporting of serious incidents and field safety corrective actions in the context of vigilance;	8.2.2, 8.2.3, 8.3.3	
(l) management of corrective and preventive actions and verification of their effectiveness;	8.5.2, 8.5.3	
(m) processes for monitoring and measurement of output, data analysis and product improvement.	8.2.5, 8.2.6, 8.4, 8.5	

MDR QMS Requirements

Chapter II

Implementing Rules

Classification governed by Intended Purpose

Article 10

General Obligations of Manufacturers

Section 9

QMS

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More MDR QMS requirements

Annex IX

Conformity Assessment Based on QMS & Technical Documentation

Chapter 1 QMS 2.2

"QMS documentation shall include …a, b, c, d, e…".

& shall grant NB access to technical documentation

MDR Annex IX QMS Requirements	ISO 13485:2016 Reference	Internal Document Reference
(a) the manufacturer's quality objectives;	4.2.1a), 5.1c), 5.3c), 5.4.1, 7.1a)	
(b) the organisation of the business and in particular:	See below indents	
— the organisational structures with the assignment of staff responsibilities in relation to critical procedures, the responsibilities of the managerial staff and their organisational authority,	5.5.1	
— the methods of monitoring whether the operation of the quality management system is efficient and in particular the ability of that system to achieve the desired design and device quality, including control of devices which fail to conform,	5.6, 7.3.5, 8.2.4, 8.3, 5.6, 8.1, 8.2.1, 8.2.4, 8.2.5, 8.2.6, 8.3, 8.4	
— where the design, manufacture and/or final verification and testing of the devices, or parts of any of those processes, is carried out by another party, the methods of monitoring the efficient operation of the quality management system and in particular the type and extent of control applied to the other party, and	4.1.5, 7.4.1	
— where the manufacturer does not have a registered place of business in a Member State, the draft mandate for the designation of an authorised representative and a letter of intention from the authorised representative to accept the mandate;	Not covered	
(c) the procedures and techniques for monitoring, verifying, validating and controlling the design of the devices and the corresponding documentation as well as the data and records arising from those procedures and techniques. Those procedures and techniques shall specifically cover:	4.2.5, 7.3	
— the strategy for regulatory compliance, including processes for identification of relevant legal requirements, qualification, classification, handling of equivalence, choice	4.1.1, 7.3.9	

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Notified Body Requirements

- Annex VII, section 4.5.2 – QMS Auditing by NB
  - Review Technical Documentation, QMS & Product Verification (4.5.3)

- Annex VII are the requirements which a NB must fulfil

- These include:
  1. Organisational & General Requirements
  2. Quality Management Requirements (internal to NB)
  3. Resource Requirements
  4. Process Requirements
  5. Unannounced audits ***must*** be performed

Where are the MDR QMS requirements?

- Use annex VII to build your internal audit criteria
- Example of content annex VII section 4.5:
  - NB must assess and identify:
    - — design and development,
    - — production and process controls,
    - — product documentation,
    - — purchasing controls including verification of purchased devices,
    - — corrective and preventive actions, including for post-market surveillance, and
    - — PMCF
  - Changes and modifications 4.9
  - Surveillance and post-cert monitoring 4.10

Where are the MDR QMS requirements?

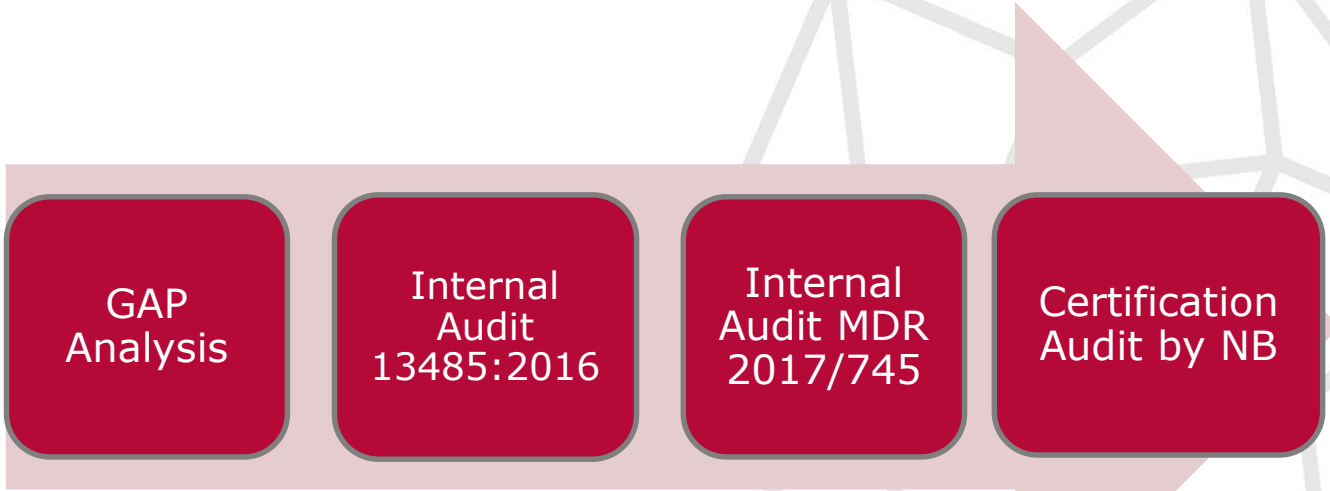
What are the "new" requirements?

Disclaimer: this list may not cover all new requirements

- Annex I, Chapter 1:
  - Section 3: (a), (b), (c), (d), (f) risk management
  - Section 4: risk management
  - Section 8: risk management

- Annex IX, Chapter 1:
  - 2.1, indent 11: procedure for keeping Clinical Evaluation Plan (CEP) up to date
  - 2.2, (b), indent 4: draft mandate for designation of Authorised Rep (AR)

Implementing the additional requirements



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Implementing the additional requirements

Consider the timing of upcoming NB ISO 13485 audits

- From date of application many MDR requirement will come into scope

If your audit is to 2016 version – medical device file will be looked at

Don’t take the additional QMS requirements in isolation – quality and regulatory must work closely

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MDR Compliance Strategy

- Current cert expiry
- NB transition plan
- NB designation & capacity
- Clinical data
- Resourcing & Competency

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Assess Systems Impact within your QMS

EUDAMED

1st rollout planned March 2020 followed by update Dec 2020

Basic UDI-DI

UDI-DI

UDI-PI

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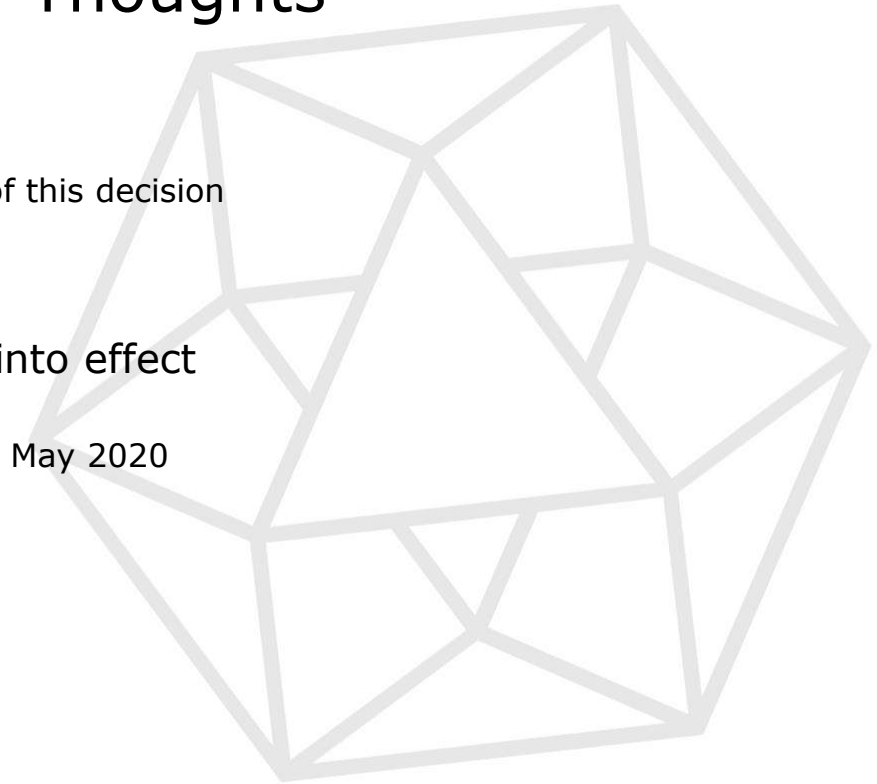
Overall Thoughts

- Decide strategy – go early – go late
  - Clinical data sufficiency is a big driver of this decision

- Consider when requirements come into effect
  - PMS requirements 26th May 2020
  - Registration of economic operators 26th May 2020
  - What's your current certificate expiry



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NB's According to current Nando

- **58 NBs** notified against directive 93/42/EEC
- **22 NBs** notified against directive 98/79/EC
- **13 NBs** notified against directive 90/385/EEC
- **1 NB** notified against MDR 2017/745 on medical devices (UK based!)

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Thank you.

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CLINICAL REQUIREMENTS FOR THE MEDICAL DEVICE REGULATION

Dr Yvonne Ndefo M.Ch.
Chief Clinical Evaluator
National Standards Authority of Ireland

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THE SECRET OF GETTING AHEAD IS GETTING STARTED
~Mark Twain~

Objectives

- Clinical Evaluation
- Equivalence
- Clinical Investigation
- Role Of The Manufacturer In Clinical Evaluation
- Must-Have Documents for Clinical Evaluation under the MDR
- Role Of The Notified Body In Clinical Evaluation
- Devices With No Intended Medical Purpose
- The Clinical Evaluation Consultation Procedure & Expert Panels
- Clinically Relevant Sections In The MDR

Clinical Evaluation

Clinical Evaluation

Clinical Evaluation is a systematic and planned process to **continuously generate, collect**, **analyse** and **assess** the **clinical data** pertaining to a device in order to **verify the safety and performance**, including **clinical benefits**, of the device when **used as intended by the manufacturer**

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Clinical Evaluation

- Clinical evaluation is necessary for demonstration of conformity with the general safety and performance requirements of the regulation
- Article 61 describes necessary requirements for performing a clinical evaluation
- The clinical evaluation, its results and the clinical evidence derived from it shall be documented in a clinical evaluation report (CER).
- The CER shall be part of the technical documentation

Clinical Evaluation

Critically evaluate scientific literature for safety, performance, design & device's intended use

CONDITIONS:

—the device is equivalent to a device to which the data relate

— the data adequately demonstrate compliance with the GSPRs

Critically evaluate results of all available clinical investigations

Consider currently available alternative treatment options (if available)

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Clinical Evaluation

- Clinical evaluation and its documentation shall be updated throughout the life cycle of the device

- Updates are performed from clinical data obtained from the manufacturer’s PMS and PMCF

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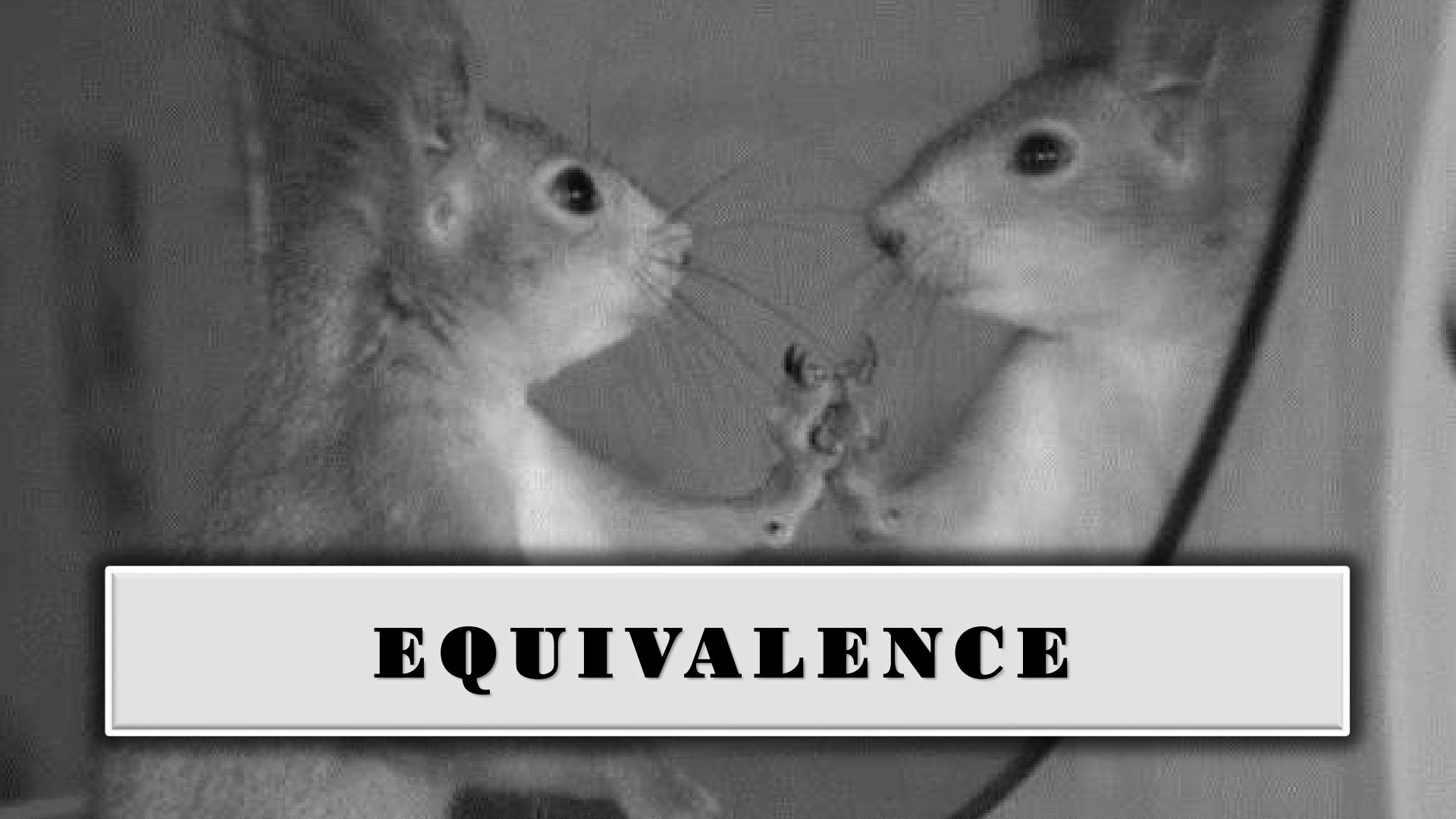

EQUIVALENCE

Equivalence

A manufacturer may perform the clinical evaluation based on clinical data relating to an equivalent device

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Equivalence

To demonstrate equivalence, **All 3 pillars must** be fulfilled

Clinical, **Technical** and **Biological** characteristics shall be taken into consideration for the demonstration of equivalence

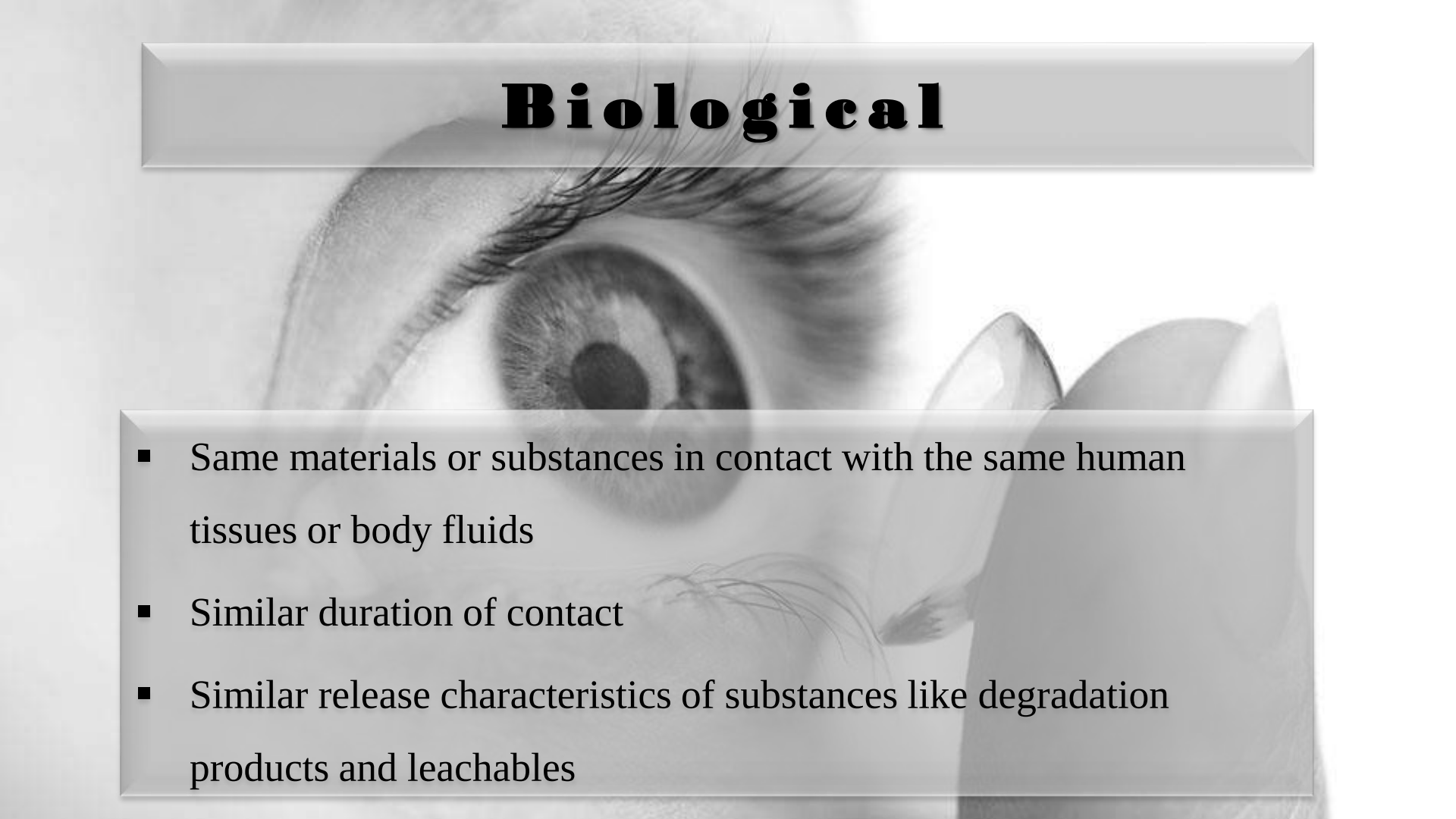
Clinical

- Same clinical condition
- Same intended purpose
- Same site in the body
- Similar population
- Similar disease severity and stage
- Does not deliver significantly different performances
- Same end-user(s)
- Similar relevant critical performance

Technical

- Similar design
- Same conditions of use
- Similar specifications and properties
- Similar surface characteristics
- Similar wavelength
- Similar software algorithms
- Similar deployment methods
- Similar principles of operation and critical performance requirements

Biological

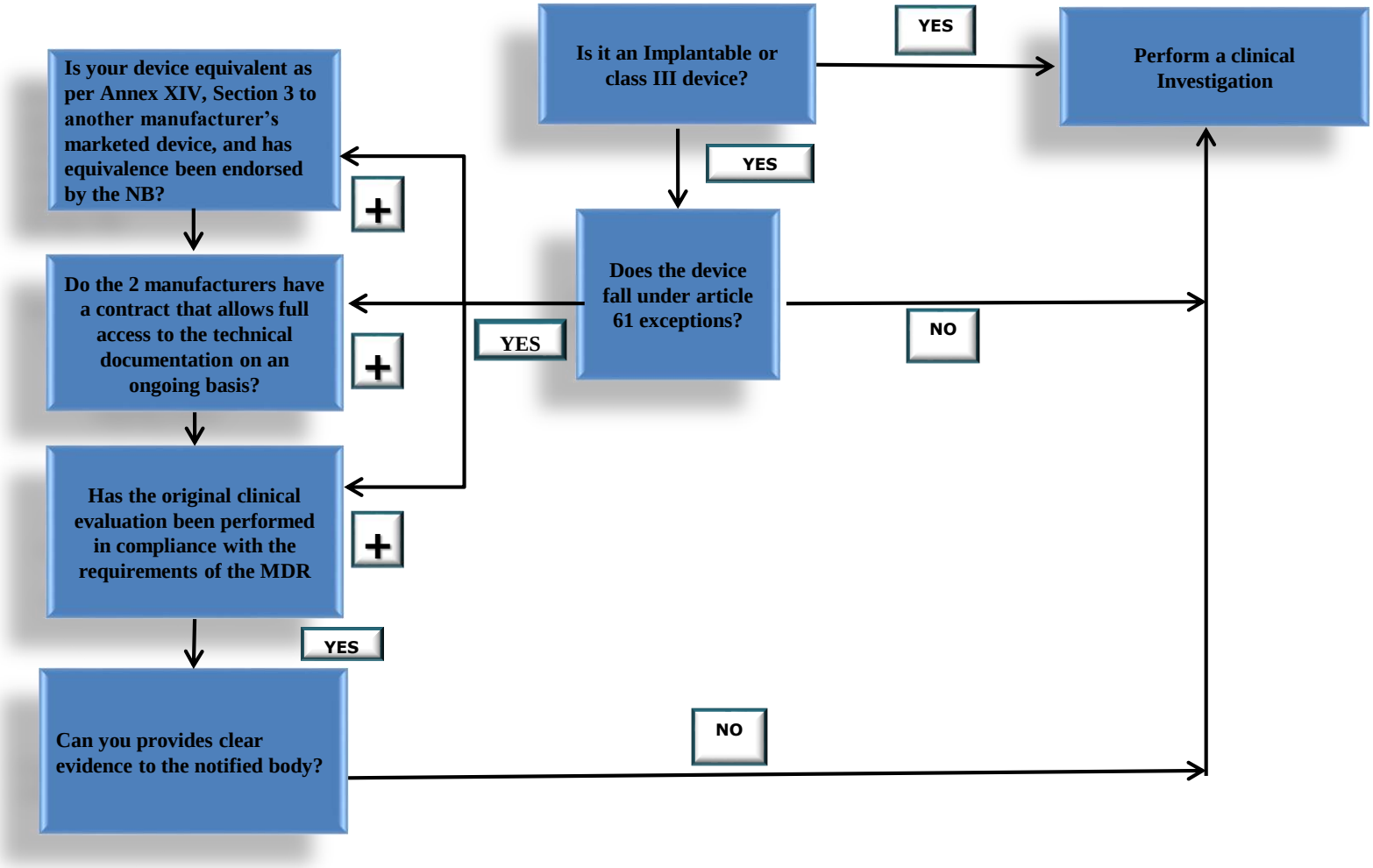


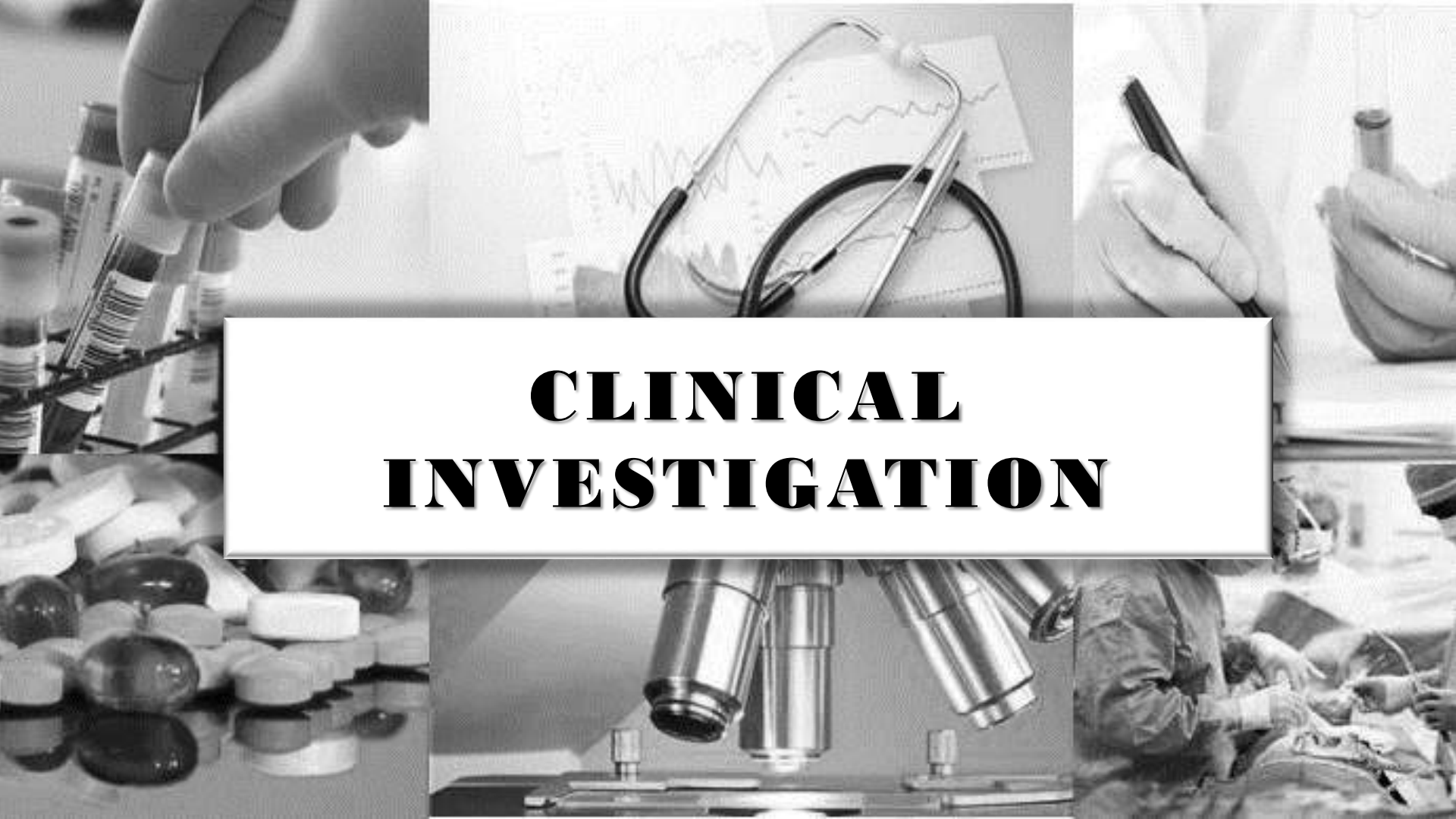
- Same materials or substances in contact with the same human tissues or body fluids
- Similar duration of contact
- Similar release characteristics of substances like degradation products and leachables

Equivalence

- There should be no clinically significant difference in the safety and clinical performance of the device

- Considerations of equivalence shall be based on proper scientific justification


Is it an Implantable or class III device?
YES
Perform a clinical Investigation
YES
Is your device equivalent as per Annex XIV, Section 3 to another manufacturer's marketed device, and has equivalence been endorsed by the NB?
+
Does the device fall under article 61 exceptions?
YES
NO
Do the 2 manufacturers have a contract that allows full access to the technical documentation on an ongoing basis?
+
Has the original clinical evaluation been performed in compliance with the requirements of the MDR
+
YES
Can you provides clear evidence to the notified body?
NO



CLINICAL INVESTIGATION

Clinical Investigation

Why should you perform a clinical investigation -

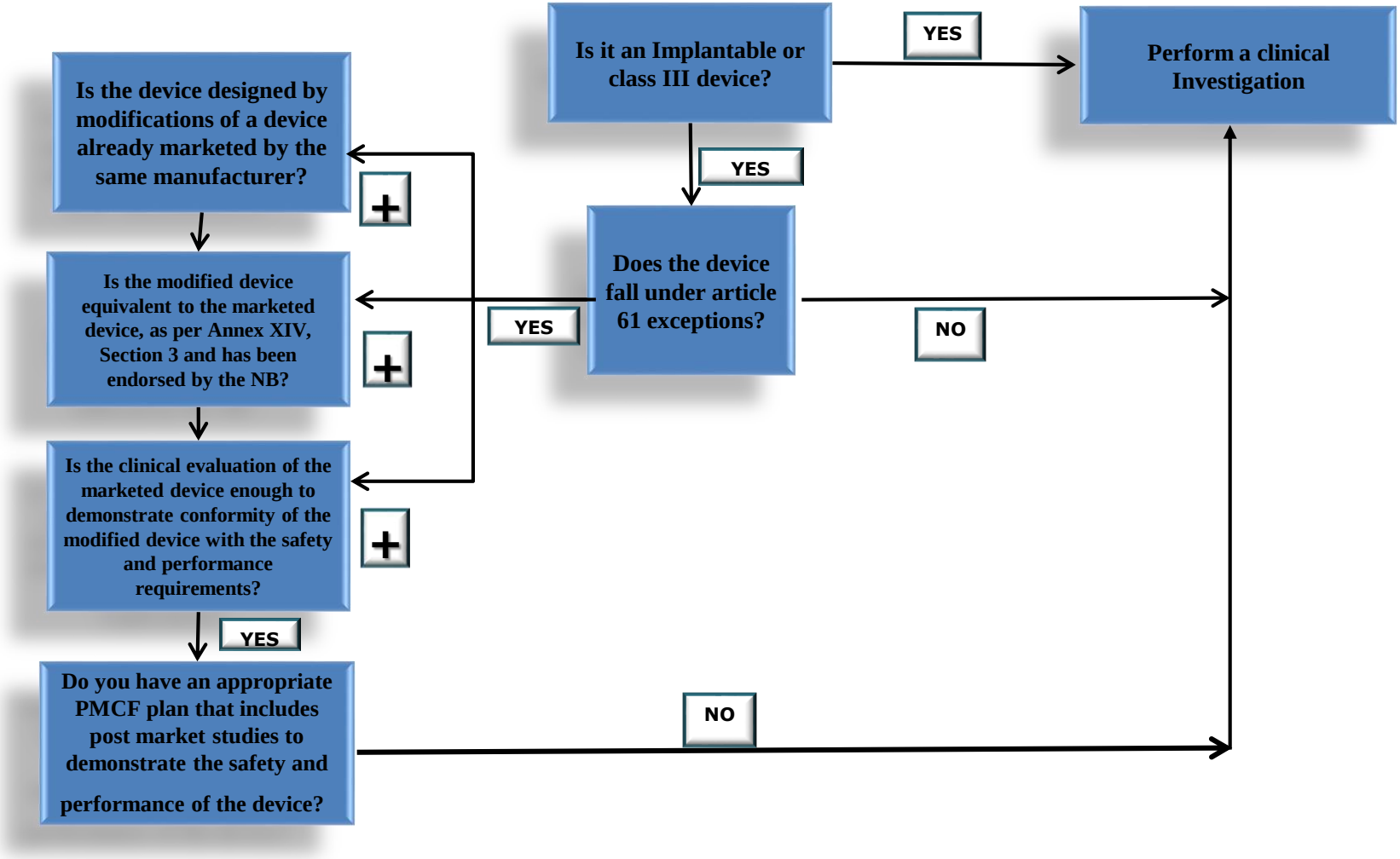
- establish & verify that, under normal conditions of use achieves the performance intended as specified by its manufacturer
- establish & verify the clinical benefits of the device
- establish & verify the clinical safety of the device
- assess if there are acceptable risks when weighed against the benefits to be achieved by the device

Clinical Investigation

Clinical investigations shall be performed for class III devices and implantable devices unless they fall under exceptions listed in chapter VI.

The investigation should -

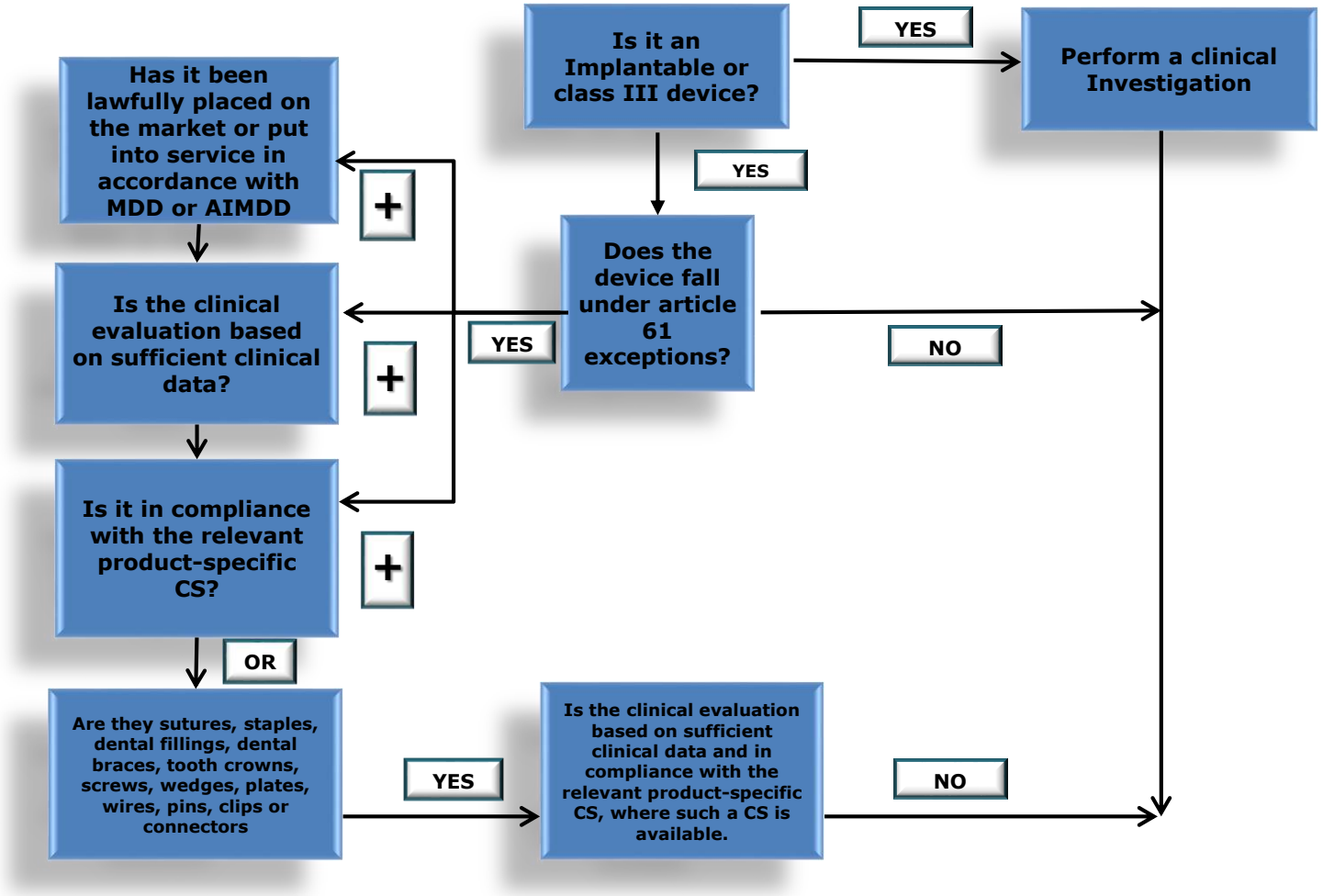
- comply with international guidance and standards- ISO 14155:2011
- align with Declaration of Helsinki on Ethical Principles
- be recorded and reported in EUDAMED
- report adverse events and device deficiencies that occur to the competent authority


Is it an Implantable or class III device?
YES
Perform a clinical Investigation
YES
Does the device fall under article 61 exceptions?
NO
YES
Is the device designed by modifications of a device already marketed by the same manufacturer?
+
Is the modified device equivalent to the marketed device, as per Annex XIV, Section 3 and has been endorsed by the NB?
+
Is the clinical evaluation of the marketed device enough to demonstrate conformity of the modified device with the safety and performance requirements?
+
YES
Do you have an appropriate PMCF plan that includes post market studies to demonstrate the safety and performance of the device?
NO

Clinical Investigation

Where devices fall under these exceptions, the NB shall verify that –

- there is an appropriate PMCF plan which includes post market studies to demonstrate the safety and performance of the device
- The manufacturer has included a justification for the exception in the CER


Is it an Implantable or class III device?
YES
Perform a clinical Investigation
YES
Has it been lawfully placed on the market or put into service in accordance with MDD or AIMDD
+
Does the device fall under article 61 exceptions?
YES
NO
Is the clinical evaluation based on sufficient clinical data?
+
Is it in compliance with the relevant product-specific CS?
+
OR
Are they sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips or connectors
YES
Is the clinical evaluation based on sufficient clinical data and in compliance with the relevant product-specific CS, where such a CS is available.
NO

Clinical Investigation

Clinical investigations shall align with the clinical investigation plan

The investigation should be performed

- with sufficient number of intended users
- in the same clinical setting, as intended when used in real life
- under normal conditions of use of the device in the same target patient population

Clinical Investigation

Endpoints shall address-

- Intended purpose
- Clinical benefits
- Performance
- Safety

All data collected in the clinical investigation is documented in the **Clinical Investigation Report**, and it shall be signed by the investigator

Clinical Investigation

- Clinical investigations which started under the MDD prior to May 26th 2020 may continue to be conducted

- From 26 May 2020, the reporting of serious adverse events and device deficiencies shall be carried out according to the MDR

Role Of The Manufacturer In Clinical Evaluation

Manufacturer's Role

In order to conform with the GSPRs, manufacturers shall

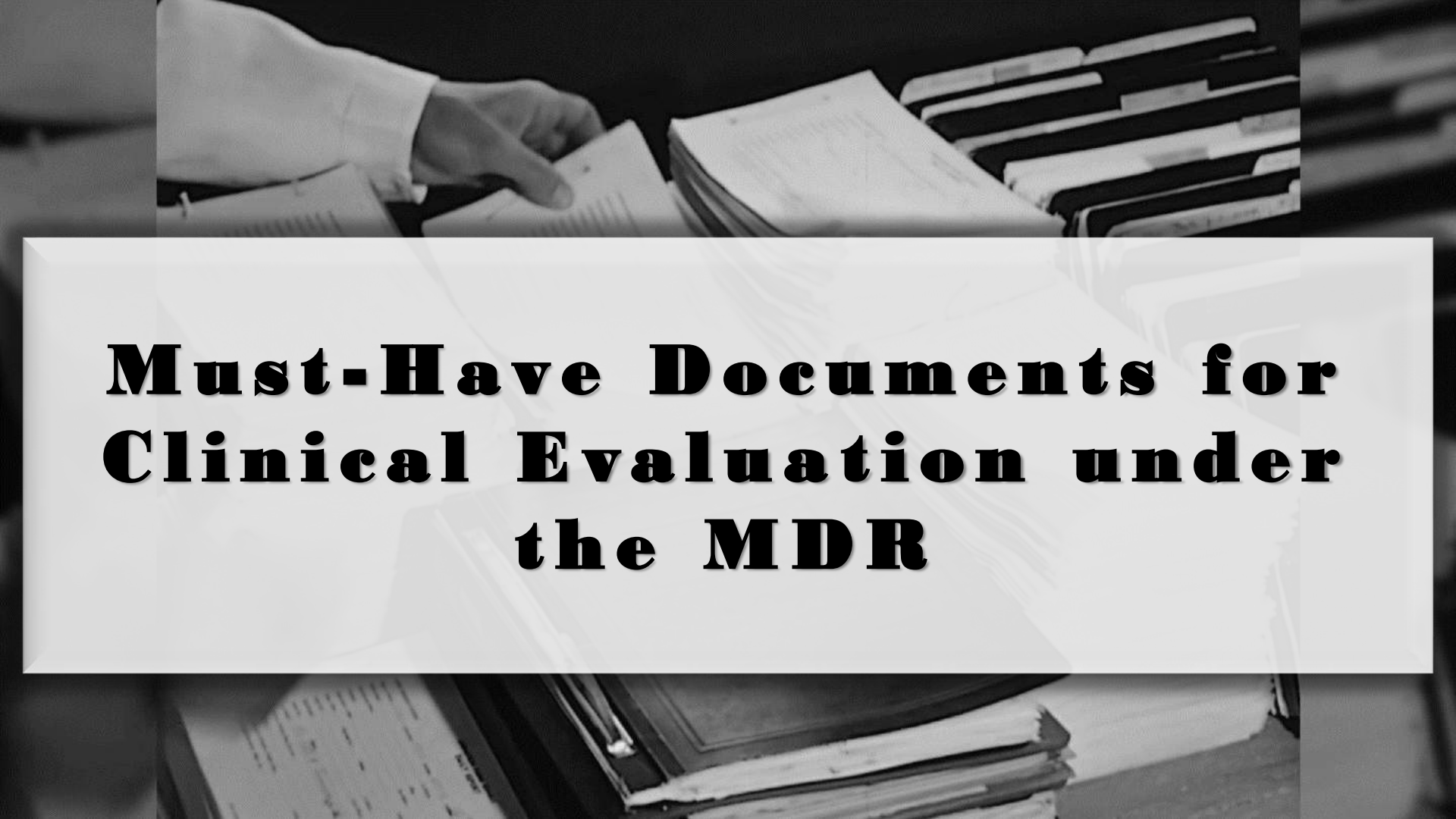
- conduct a clinical evaluation in compliance with Article 61 and Annex XIV
- plan, continuously conduct and document a clinical evaluation
- specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant GSPRs

Manufacturer's Role

- It is the manufacturer's obligation to perform a clinical evaluation
- Manufacturer's **cannot** demonstrate conformity to the GSPRs without a clinical evaluation

Class III Implantable Devices And Class IIb Active Devices Intended To Administer Medicinal Substances

- MFRs can choose to consult an expert panel prior to its clinical evaluation and/or investigation
- Expert panel shall review the MFR's clinical development strategy and clinical investigation proposals.
- MFRs shall consider the views of the expert panel and document this in the clinical evaluation report.
- The expert panel's view will not apply to future conformity assessment procedures



Must-Have Documents for Clinical Evaluation under the MDR

1. Clinical Evaluation Plan (CEP)

The CEP shall–

- Include identification of MFRs GSPRs
- Specify the intended use and intended target groups of the device
- Specify the indications and contra-indications
- Include intended clinical benefits
- Specify the methods used to determine clinical safety
- Include parameters used to determine acceptability of benefit-risk ratio
- Specify how the benefit-risk issues will be addressed
- Include a **clinical development plan**

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2. Clinical Evaluation Report (CER)

- Comprises of all results of the clinical evaluation
- All Clinical evidence to support the safety and performance of the device should be in the CER
- Includes both favourable and unfavourable data
- Includes PMS and PMCF data

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3. Summary of Safety and Clinical Performance (SSCP)

- For implantable devices and for class III devices
- Should be clear to the intended user and/or the patient for transparency
- Made available to the public in Eudamed
- Should be submitted to the NB
- Annually updated

4. Clinical investigation documents (if applicable)

- Clinical Investigation Plan
- Investigator's Brochure
- Clinical Investigation Report

5. Literature Search Protocol And Report

- Source of clinical data
- A search for articles published in peer reviewed scientific literature on clinical experience of the device or equivalent devices
- Used to support the safety, performance, design characteristics and intended purpose of the device
- NB will review the literature search methodology and documentation from the literature search

6. PMS Plan

The post-market surveillance plan shall include-

- a process that allows description of the performance of the devices
- comparison between the device and similar products in the market
- methods to assess the collected data
- methods to investigate complaints and analyse market experience
- methods to manage the events subject to the trend report
- methods to communicate effectively with competent authorities, notified bodies, economic operators and users
- PMCF Plan

7. PMCF Plan

- Continuous process which updates the clinical evaluation
- Is conducted by proactively collecting and evaluating clinical data from the marketed device
- Is aimed at confirming the safety and performance throughout the expected lifetime of the device
- It ensures continued acceptability of identified risks and detects emerging risks in real life clinical setting
- It aids in assessing the need for preventive and/or corrective measures

8. PMCF Evaluation Report (PMCFER)

- Includes results of the findings of the PMCF
- Is part of the CER and technical documentation
- The conclusions of the PMCFER shall be taken into account for the clinical evaluation

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9. Periodic Safety Update Report (PSUR)

- Manufacturers of class IIa, class IIb and class III devices shall prepare a PSUR
- Part of the technical documentation
- Includes summary of results and conclusions of the PMS data
- PSURs shall be updated at least annually for class IIb and class III devices
- PSURs shall be updated at least biennially for class IIa devices

9. Periodic Safety Update Report (PSUR)

- PSURs for class III devices or implantable devices, shall be submitted to the NB via EUDAMED
- PSURs for class IIa and class IIb non-implantable devices shall be made available to the NB, and to the competent authorities on request
- The NB shall review the report and add its evaluation, with details of any action taken to EUDAMED
- This shall be made available to competent authorities via EUDAMED

Relevant Documents for Clinical Review under the MDR

Pre – CE Mark	Post – CE Mark
CEP (Includes the Clinical Development Plan)	CEP (Includes the Clinical Development Plan)
CER	CER
SSCP (for implantable and class III devices)	SSCP (for implantable and class III devices)
Supporting documents for equivalence, if applicable (includes contract, equivalent device technical file)	PMS Plan
Clinical Investigation documents, if applicable (includes CI Plan, CI brochure, CI report)	PMCF Plan
Literature search protocol and report	PMCF Evaluation Report (Annual updates for implantable and class III devices)
	PSUR (updated annually for Class IIb & Class III, and biennially for class IIa Devices)
	Literature search protocol and report

*** ***Additional supporting documents may be required***

Role Of The Notified Body In Clinical Evaluation

Role Of The Notified Body

During assessment of the Clinical Evaluation, the NB shall focus on-

- intended use and claims for the device
- methodology of the literature search
- relevant documentation from the literature search
- clinical investigation
- validity, demonstration, suitability and conclusions data from equivalent devices
- post-market surveillance and PMCF
- planning of the clinical evaluation(CEP)
- CER

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Role Of The Notified Body

NB will ensure that the:

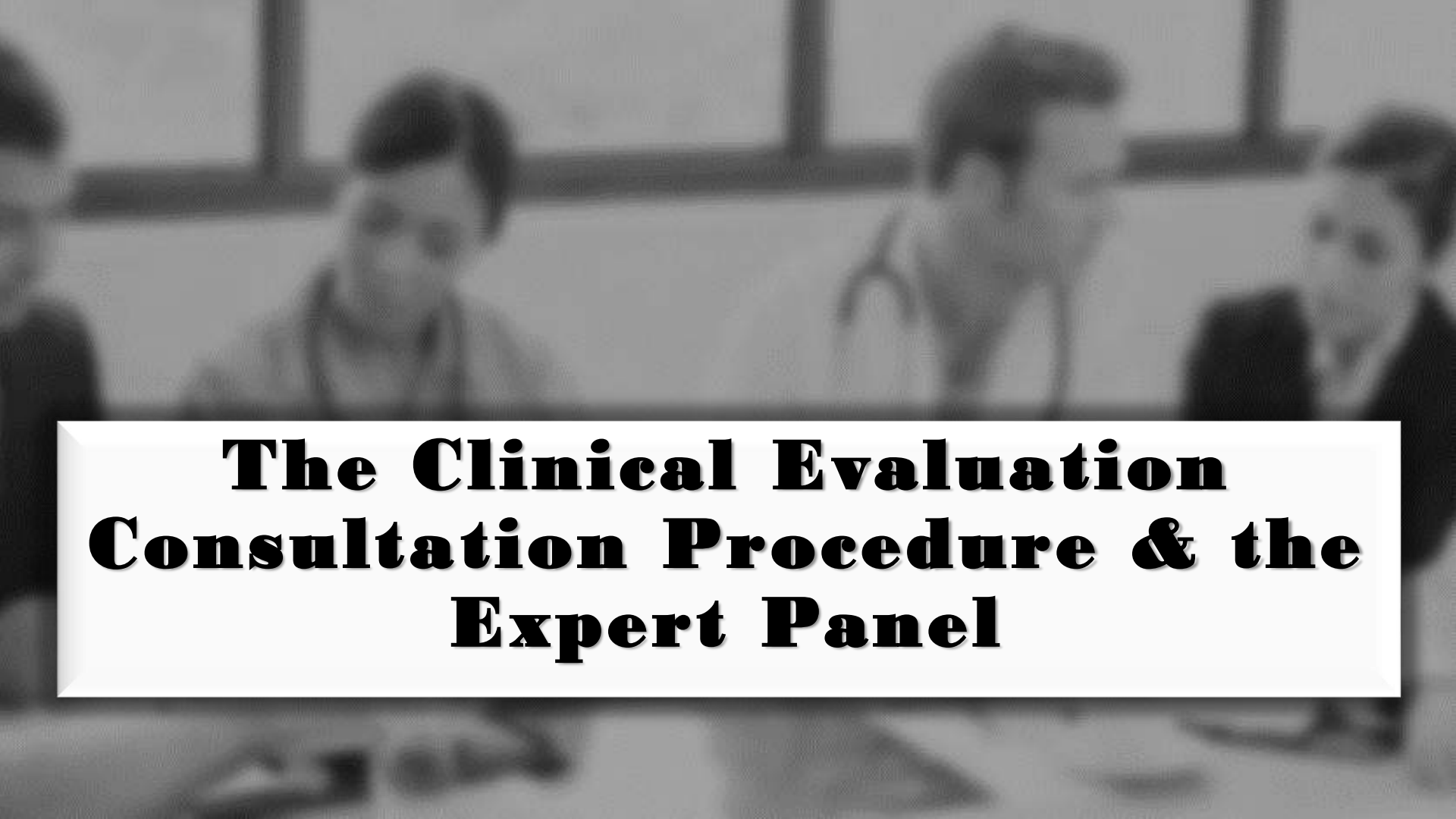
- clinical evaluation adequately addresses the GSPRs
- clinical evaluation aligns with the risk management requirements is reflected in the IFU
- specific claims are supported by specific pre-clinical and clinical data and risk analysis
- The NB shall provide the manufacturer with a report on the clinical evaluation assessment called a **Clinical Evaluation Assessment Report (CEAR)**

Devices With No Intended Medical Purpose (Annex XVI Devices)

- Contact lenses & other devices inserted in the eye
- Surgically invasive devices that modify the anatomy or fix body parts
- Dermal or mucous membrane fillers
- Devices used to reduce, remove or destroy adipose tissue, such e.g liposuction, lipolysis or lipoplasty equipment
- Devices emitting high intensity electromagnetic radiation e.g lasers for skin resurfacing, tattoo or hair removal
- Deep brain stimulation devices that modify neuronal activity in the brain.

MFR shall demonstrate the performance of these devices

- Clinical evaluations of those products shall be based on-
- Safety data
- Post-market surveillance data
- PMCF
- Clinical investigation



The Clinical Evaluation Consultation Procedure & the Expert Panel

Consultation Procedure For Class III Implantable And Class IIb Devices

For class III implantable devices class IIb active devices intended to administer and/or remove a medicinal product

- The expert panel shall decide whether to provide a scientific opinion on the -
  - CEAR of the notified body
  - benefit-risk determination
  - consistency of the clinical evidence with the medical indication(s)
  - PMCF plan

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The NB sends CEAR + CER + CEP + PMCF plan + PMCFER to the Commission.

Commission shall immediately transmit those documents to the relevant Expert Panel

The NB may be requested to present its conclusions to the expert panel concerned.

Within 21 days the Expert Panel shall notify the Commission on decision to provide a scientific opinion

Within 60 days, the Expert panel shall their provide scientific opinion

Consultation Procedure For Class III Implantable And Class IIb Devices

Class III implantable devices and class IIb active devices intended to administer and/or remove a medicinal product, **do not require** expert panel consultation during:

- Device Recertifications under the MDR
- Significant change applications
- Where common specifications apply, and the notified body confirms that the clinical evaluation for the device is in compliance with the relevant CS for that kind of device.

Relevant sections in the for clinical requirements and post market clinical follow up

Relevant sections in the MDR discussing clinical requirements are -

- Article 32 - Summary of safety and clinical performance
- Article 54 - Clinical evaluation consultation procedure for certain class III and class IIb devices
- Chapter VI, Article 61- Clinical Evaluation
- Chapter VI, Article 61- 82- Clinical investigation
- Annex XIV, Part A- Clinical Evaluation
- Annex XIV, Part B- Post market Clinical Follow-up
- Annex XV - Clinical Investigations

Thank you.

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- What practical steps are companies taking to prepare for Brexit?
- What supports are available to companies?
- No regrets planning?

What practical steps are companies taking to prepare for Brexit?

Assess areas of potential risk

UK market dynamics	Currency	Customers
Competition	Sourcing	Customs & logistics
Regulations & standards	Tariffs and VAT	Movement of people

Brexit Scorecard

www.prepareforbrexit.ie

What supports are available to companies?

1. Advisory

2. Financial Support

Enterprise Ireland

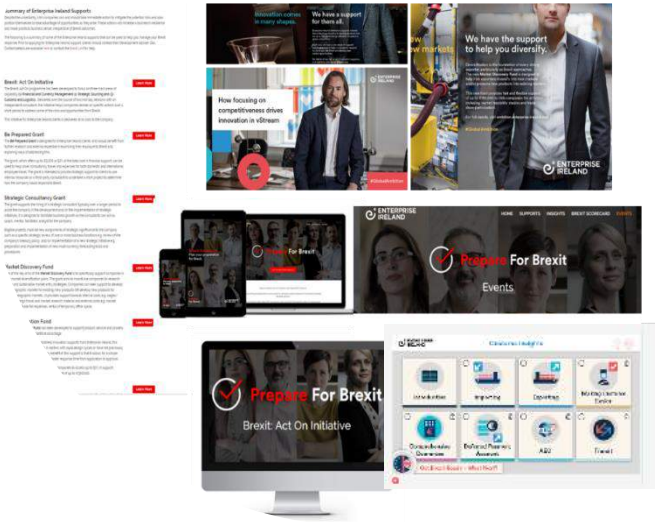
- Brexit Advisory Clinics
- www.prepareforbrexit.ie
- Online Customs Insights course
- Webinars

IntertradeIreland

- Tariff Tracker
- Simple Guide to doing Cross Border business
- Research Reports

Local Enterprise Office

- Lean for Micro
- Management Development Programmes



The €300m Government of Ireland Brexit Loan Scheme

Strategic Banking Corporation of Ireland
www.sbci.gov.ie

Enterprise Ireland

- Act On & Be Prepared Supports
- Strategic Consultancy

IntertradeIreland

- Start to Plan Vouchers programme
- Sales programmes - Acumen, Elevate and TAV programmes
- Innovation programmes – Fusion, Challenge and Co-Innovate programmes

Local Enterprise Offices

- Trading Online Voucher Scheme
- Technical Assistance for Micro Exporters
- Agile Innovation Fund

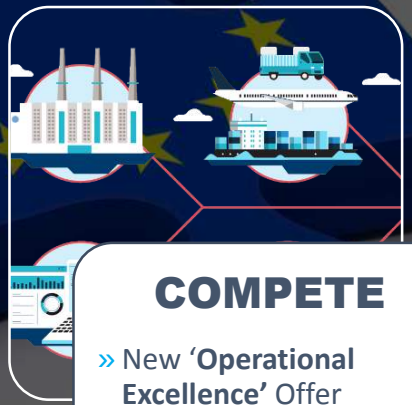
No Regret Planning ....

INNOVATE

- New '**Agile R&D Fund**'
- **Horizon 2020** funding
- Access to Technology Gateways
- Regional Technology Centres

DIVERSIFY

- New '**Market Discovery**' Fund
- Eurozone Strategy
- ↑Trade Missions
- Overseas offices (33)
- **'Irish Advantage'** Campaign



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