



## BSI Medicines & Biologics

Dr Jennifer Durrant  
Global Head, Medicinal & Biologics Team



# Agenda

BSI Medical Devices Team

BSI Medicinal & Biologics Team

MDR Impact

- Combination Products
- Devices Utilising Materials of Biological Origin
- Devices Composed of Substances
- Active Devices Intended to Administer Medicines
- IVF/ART



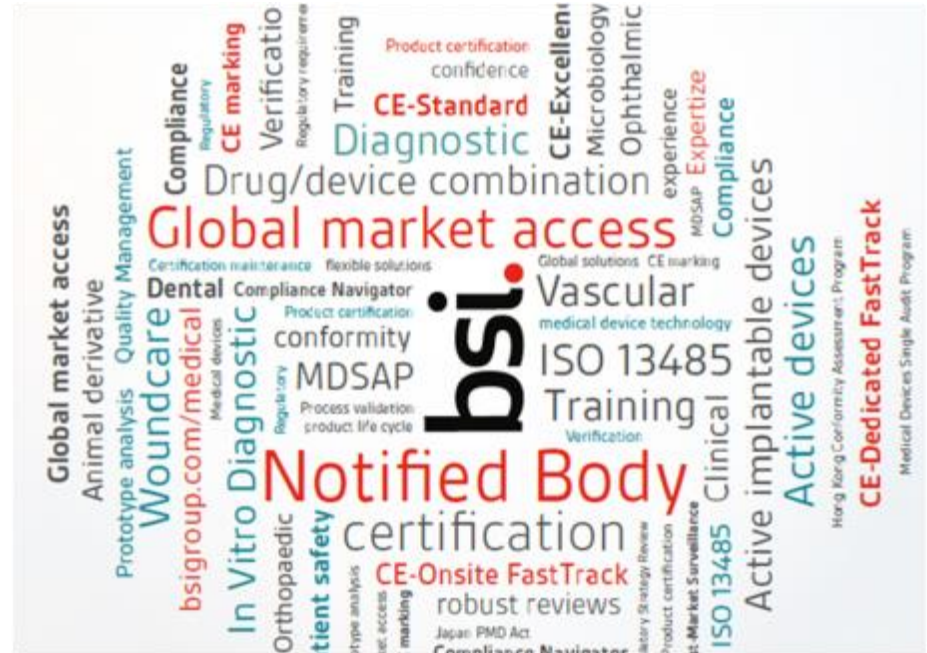
# BSI Medical Devices

# BSI Medical Devices – What we do

## Our mission

We ensure **patient safety** while supporting **timely market access** for our clients' medical device products **globally**.

We provide our customers with **thorough, responsive, predictable** conformity assessments, evaluations and certifications that are recognized and accepted **worldwide**.



# About BSI Medical Devices

96%

**96% of the world's top 25**  
medical device manufacturers work with BSI

500+

**Over 500**  
colleagues worldwide

**Market leader**

**Largest Notified Body**  
globally; BSI is a market leader

**Full scope  
Notified Body**

**Designated with full scope**  
to the MDD, AIMDD, IVDD **and MDR**

**Designated and  
Accredited**

**Designated by** MHRA, IGJ  
**Accredited by** UKAS, SCC and RvA  
**Recognized by** MHLW/PMDA, TFDA, MDB, INMETRO,

## BSI in The Netherlands

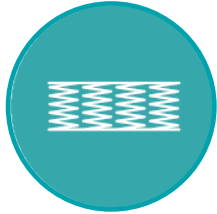
- Achieved ISO 13485 Accreditation under the Dutch Accreditation Council (RVA).
- Designated with full scope to the MDD, AIMDD, IVDD (IGJ)
- MDR joint designation audit was completed early 2019

# BSI Medical Devices - Industries covered



## Orthopaedic Devices

Joints, implants & cements



## Vascular Devices

Heart valves, vascular grafts & stents



## Active Devices

Medical imaging equipment, patient monitors & incubators



## Microbiology and sterile devices

Devices, packaging & processes



## In Vitro Diagnostic Devices

Pregnancy tests, blood glucose monitors & HIV tests



## Dental Devices

Dental implants, coatings & instruments



## Active Implantable Devices

Pacemakers, neurostimulators & radiation therapy devices



## General Devices

Woundcare devices, ophthalmic devices, IVF devices & contraceptive devices



## Devices utilizing animal tissue

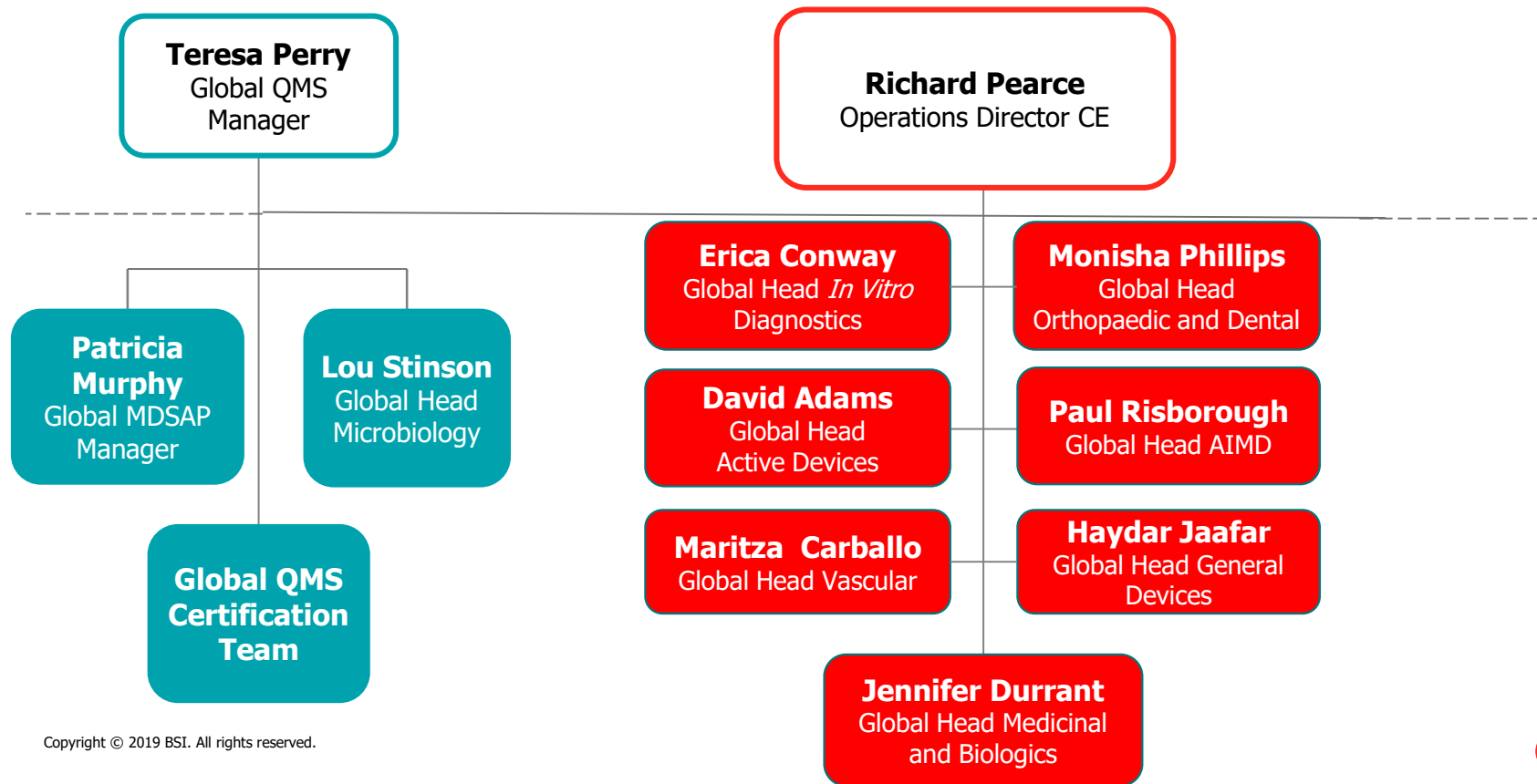
Bone void fillers, dural grafts & haemostats



## Device-Drug Combinations

Drug eluting stents, wound dressings & sutures

# BSI Medical Devices – Our team



**bsi.**

# BSI Medicinal and Biologics team



**bsi.**

Copyright © 2019 BSI. All rights reserved.



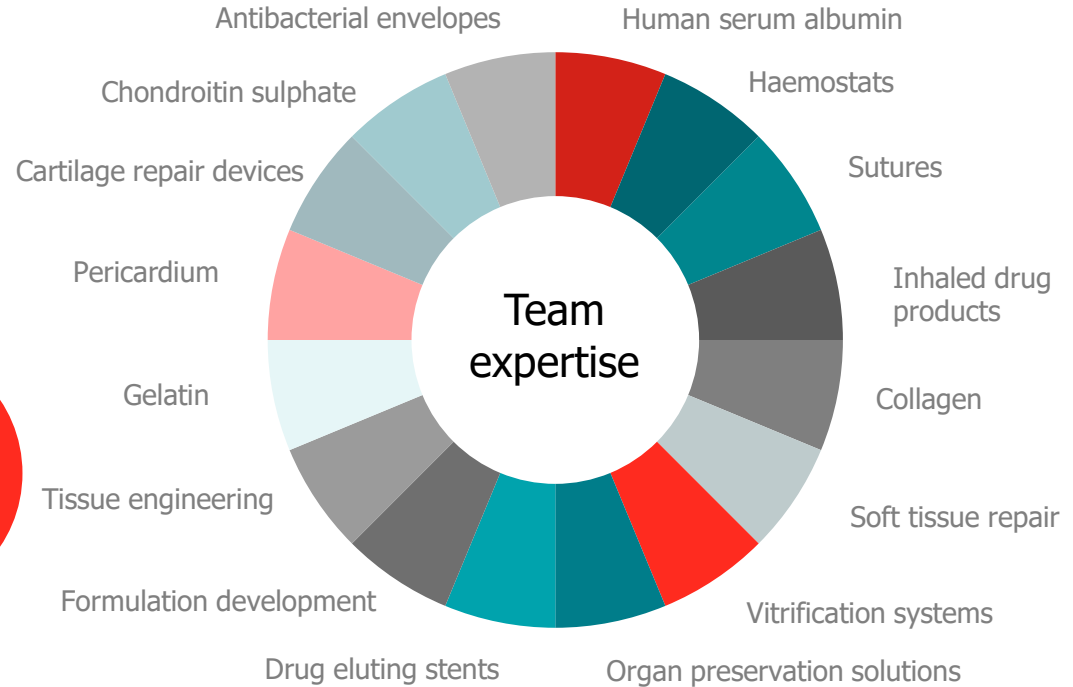


# Unrivalled expertise from BSI's Medicinal and Biologics team

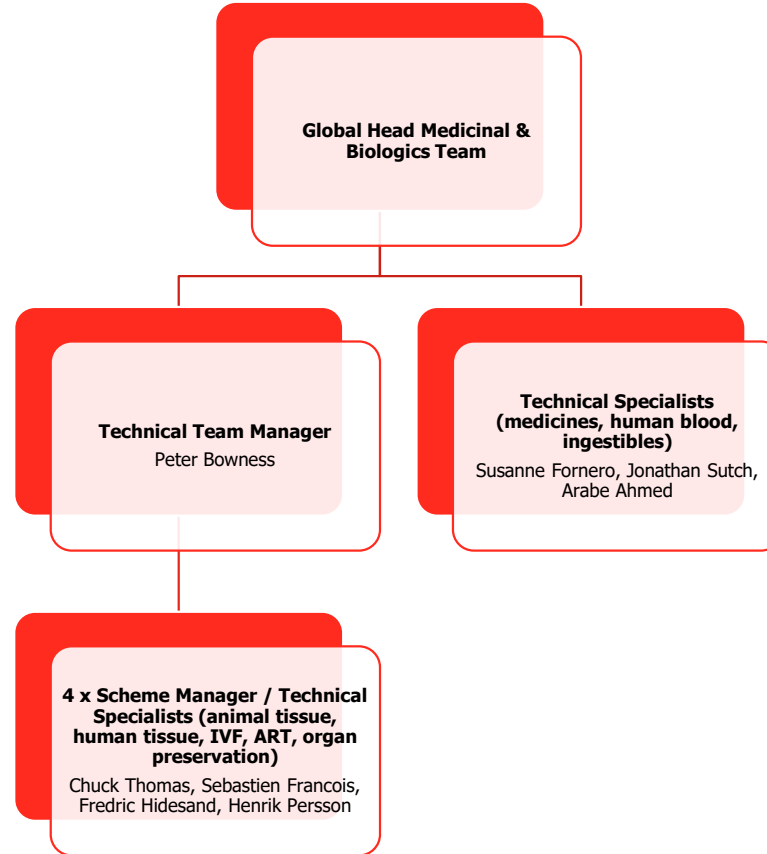
- The BSI Medicinal and Biologics team is made up of specialists with expertise in devices utilizing biological substances, medicinal substances and IVF/ART devices.
- The team have over 14 graduate degrees between them.

The BSI Medical Devices Medicinal and Biologics team combined experience

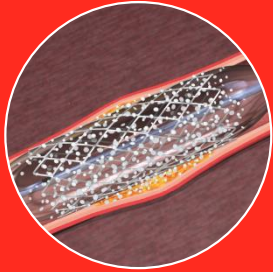
**107**  
YEARS



# Medicinal & Biologics Team Structure:



# Medicinal & Biologics Team Scope



Device-drug  
Combinations



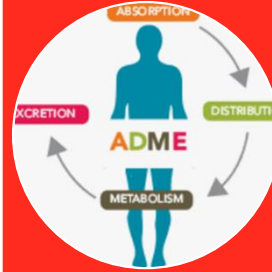
Drug-device  
combinations



Devices  
utilising  
materials of  
biological  
origin



IVF/ART,  
Organ  
Preservation



Devices  
Composed of  
Substances



Active  
devices  
intended to  
administer  
medicines



# Medicinal & Biologics Team Delivery



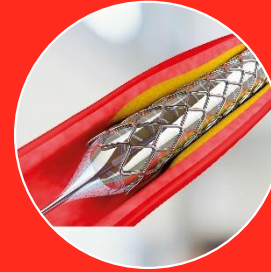
Active  
Devices  
Team



General  
Devices  
Team



Orthopaedic  
& Dental  
Team



Vascular  
Team



Active  
Implantable  
Team

**Medicinal & Biologics Team**



# MDR Impact

# New Regulations for medical devices

The new European Union Medical Devices Regulation (MDR) is replacing the Medical Devices and Active Implantable Medical Devices Directives (MDD and AIMDD).

Medical Devices Directive  
93/42/EEC

Active Implantable Medical  
Devices Directive  
90/385/EEC



Medical Devices Regulation  
EU 2017/745

# New Regulations for medical devices

- The Medical Devices Regulation (MDR) entered into force on **25 May 2017**.
- The MDR has a **three year** transition period.
- Manufacturers have the duration of the transition period to **update** their technical documentation and processes to meet the **new requirements**.

BSI was in the first wave of Notified Bodies to apply for designation to both the Medical Devices Regulation and the IVD Regulation to the UK and Dutch Competent Authorities.

# MDR timelines

**25 May 2017**

Entry into Force

**3 year transition period**

**26 May 2020**

Date of application

MDD/AIMDD  
certificates can no  
longer be issued

**27 May 2022**

Annex VI certificates  
no longer valid

**27 May 2024**

MDD/AIMDD  
certificates no  
longer valid

**27 May 2025**

Devices under MDD/  
AIMDD can no  
longer be placed on  
the market

MDD / AIMDD certificates maintain validity during this period; renewals allowed but will be issued with limited validity

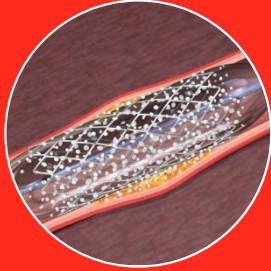
MDR certificates valid

**26 Nov 2017**

NBs can apply for designation



# MDR Impact



Device-drug  
Combinations



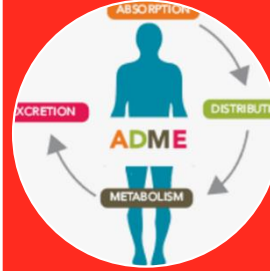
Drug-device  
combinations



Devices  
utilising  
materials of  
biological  
origin



IVF/ART,  
Organ  
Preservation



Devices  
Composed of  
Substances



Active  
devices  
intended to  
administer  
medicines

**Significant impact for clients who wish to place  
these products on the market**

A thick teal arc curves across the top and right side of the slide, starting from the left edge and ending near the bottom right corner.

## Device-Drug Combinations

# Classification

## **MDD Rule 13**

All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 2001/83/EC, and which is liable to act on the human body with action ancillary to that of the devices, are in Class III.

## **MDR Rule 14**

All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma, as defined in point 10 of Article 1 of that Directive, and that has an action ancillary to that of the devices, are classified as class III.

A thick teal arc curves across the top and right side of the slide, starting from the left edge and ending near the bottom right corner.

## Drug-Device Combinations

# Article 117 of MDR



In Annex I to [Directive 2001/83/EC](#), point 12 of Section 3.2. is replaced by the following

**bsi.**

# Current Status (Under MDD and current 2001/83/EC)

## Drug Device Manufacturers:

- Essential requirements of Annex I MDD applies to the device component for safety and performance features
  - Reference Article 1 (3) of the 93/42/EEC
  - However,
    - No text contained in Directive 2001/83/EC;
    - No details on what was expected and how the assessment to Annex I of MDD was to be conducted
- No Notified Body involvement**
- Inconsistent Competent Authorities scrutiny



## Article 117



### Amendment to Directive 2001/83/EC

In Annex I to Directive 2001/83/EC, point 12 of Section 3.2. is replaced by the following:

‘(12) Where, in accordance with the second subparagraph of Article 1(8) or the second subparagraph of Article 1(9) of Regulation (EU) 2017/745 of the European Parliament and of the Council (\*), a product is governed by this Directive, the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation contained in the manufacturer’s EU declaration of conformity or the relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device.

If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) 2017/745, the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body designated in accordance with that Regulation for the type of device in question.

# Examples in scope

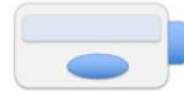
Pre-filled  
Syringe



Pre-filled  
Injector/ pen



Novel pre-filled  
device



Transdermal  
contraceptive  
patch



Metered dose  
inhaler  
(combined)



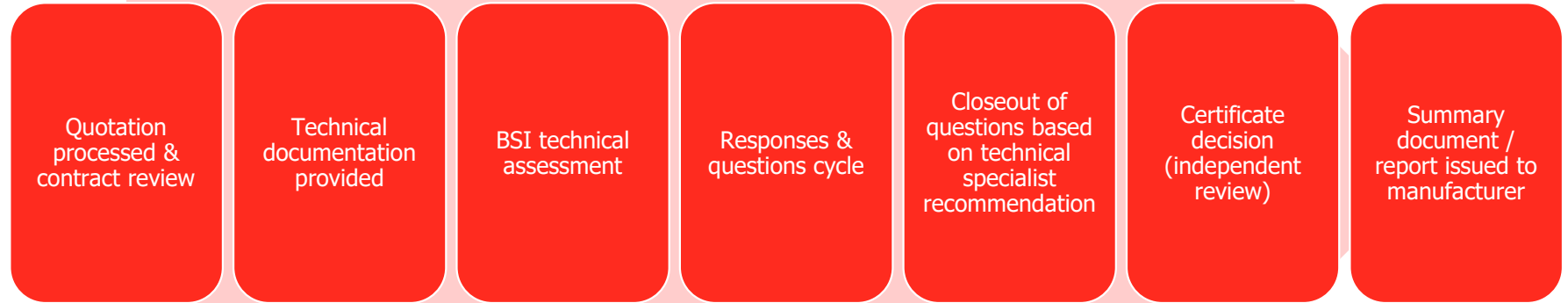


# Impact of Article 117 on Pharmaceutical Industries

- The **relevant** General Safety and Performance Requirement (GSPR) of MDR Annex I will apply to the device component.
- Need to find & work with a designated Notified Body
- Obtain Notified Body assessment report
- Include this assessment report in the MAA
- No grandfathering so theoretically **26th May 2020**
- **In case of changes to device**, Notified Body reassessment required for significant change to the device

# Notified Body Assessment: Article 117

## BSI Review Process:



# Notified Body Assessment: Article 117




















## General Safety and Performance Requirements (Annex 1)

**Chapter 1:  
General  
Requirements**  
(SPRs 1-9)

**Chapter 2:  
Design and  
Manufacture**  
(SPRs 10-22)

**Chapter 3:  
Information  
Supplied with the  
Device (SPR 23)**

# Annex I – Safety and performance requirements

- |    |  |   |   |     |  |   |     |  |   |
|----|--|---|---|-----|--|---|-----|--|---|
| 1. | Safe, Perform as Intended, State of the Art                              |  |  | 10. | <b>Chemical, Physical &amp; Biological Properties</b>  |  | 17. | <b>Electronic programmable systems</b>   |  |
| 2. | Risk reduction as far as possible  |   |   | 11. | Infection & Microbial Contamination  |  | 18. | Active devices and devices connected to them   |  |
| 3. | <b>Risk Management</b>   |  |   | 12. | Devices incorporating a medicinal product and devices composed of substances that are absorbed by or locally dispersed in the human body |   | 19. | Requirements for AIMD  |  |
| 4. | Risk Control   |   |   | 13. | Devices incorporating <b>materials of biological origin</b>  |  | 20. | Protection against mechanical and thermal risks  |   |
| 5. | Risk of <b>Use Error</b>   |  |   | 14. | Construction and <b>interaction with the environment</b>   |   | 21. | Protection against the risks posed to the patient or user by supplied energy or substances |  |
| 6. | Lifetime   |  |   | 15. | Devices with a diagnostic or measuring function  |  | 22. | Protection against the risks posed by medical devices intended for use by lay persons      |  |
| 7. | Packaging, Transport, Storage  |  |   | 16. | Protection against radiation   |  | 23. | <b>Information Supplied</b>  |  |
| 8. | Undesirable side-effects minimised & Risks < Benefits                    |   |   |     |  |   |     |         |   |
| 9. | Annex XVI “no risk at all” or “no more than the maximum acceptable risk” |  |   |     |  |   |     |  |   |

# Notified Body Assessment: Article 117

## Annex II: Technical Documentation

### 4. GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

The documentation shall contain information for the **demonstration of conformity with the general safety and performance requirements** set out in Annex I that are **applicable to the device taking into account its intended purpose**, and shall include **a justification, validation and verification of the solutions adopted** to meet those requirements. The demonstration of conformity shall include:

- (a) the general safety and performance requirements that apply to the device and an explanation as to why others do not apply;
- (b) the method or methods used to demonstrate conformity with each applicable general safety and performance requirement;
- (c) the harmonised standards, CS or other solutions applied; and
- (d) the precise identity of the controlled documents offering evidence of conformity with each harmonised standard, CS or other method applied to demonstrate conformity with the general safety and performance requirements. The information referred to under this point shall incorporate a cross-reference to the location of such evidence within the full technical documentation and, if applicable, the summary technical documentation.

# Notified Body Assessment Report

- The NB assessment report will provide details on:
- The evidence assessed by the NB, including reference to key reports
- Detail the technical characteristics of the device including drawings / specifications
- Summarise how the manufacturer has demonstrated conformity with requirements
- A clear NB conclusion with confirmation of acceptability / or not with reference to applicable requirement



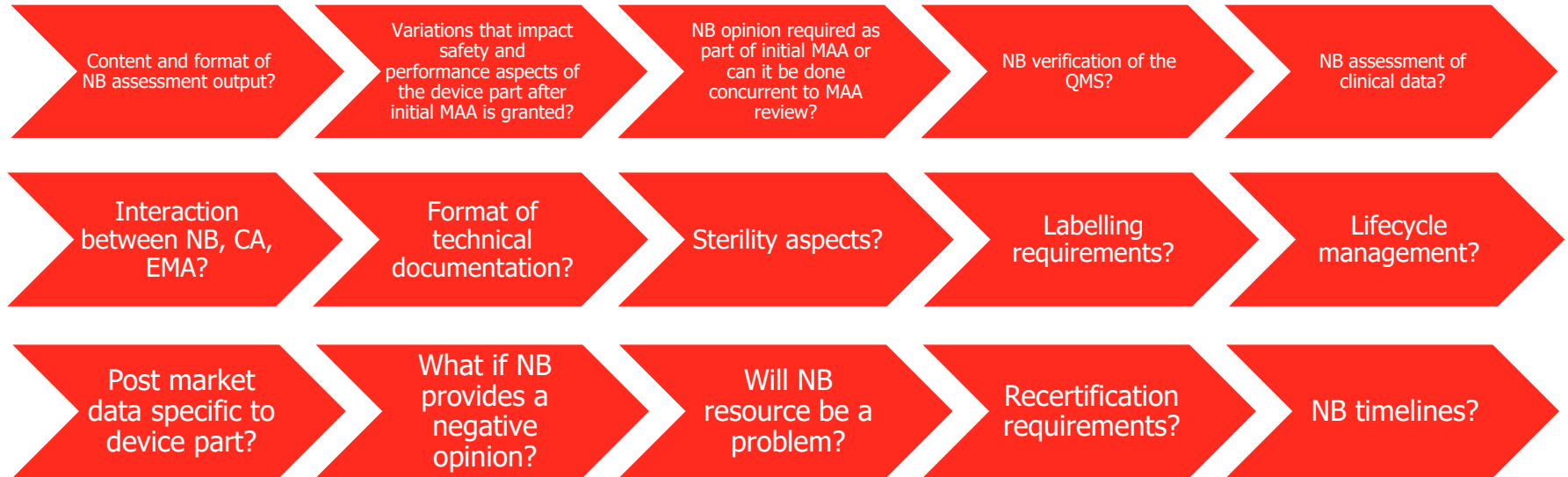
# Notified Body Assessment of Changes

- MAA Holders must manage device changes and consider impacts
- Foresee NB involvement in assessment of changes, examples include;
- Changes that impact device safety or performance
- Device design change impacting usability
- Product formulation changes
- Intended use of the device / change to medicinal product



# (EU) 2017/745 – Article 117

## Just some of the challenges.....





# (EU) 2017/745 – Article 117

## Some progress has been made...

QWP/BWP Guideline expected soon

Team NB Working Group for Article 117 established

NB-published guidance on requirements for technical documentation, safety and performance requirements

## Summary:

- MDR will apply from **26th of May 2020**
- MDR designation process for Notified Bodies is ongoing
- NB will only be able to accept application:
  - **once designated under MDR** (<http://ec.europa.eu/growth/tools-databases/nando/>)
  - **if scope of designation covers the type of device in question**
- Many unanswered questions regarding Article 117 process...
- NB workload is increasing.....
- Speak to NB early to understand if and when they can accept the application
- Factor in these activities and associated timelines in project planning



Devices utilising materials of  
biological origin

# Classification

## **MDD Rule 17**

All devices manufactured utilizing animal tissues or derivatives rendered non-viable are Class III except where such devices are intended to come into contact with intact skin only.

## **MDR Rule 18**

All devices manufactured utilising tissues or cells of human or animal origin, or their derivatives, which are non- viable or rendered non-viable, are classified as class III, unless such devices are manufactured utilising tissues or cells of animal origin, or their derivatives, which are non-viable or rendered non-viable and are devices intended to come into contact with intact skin only.

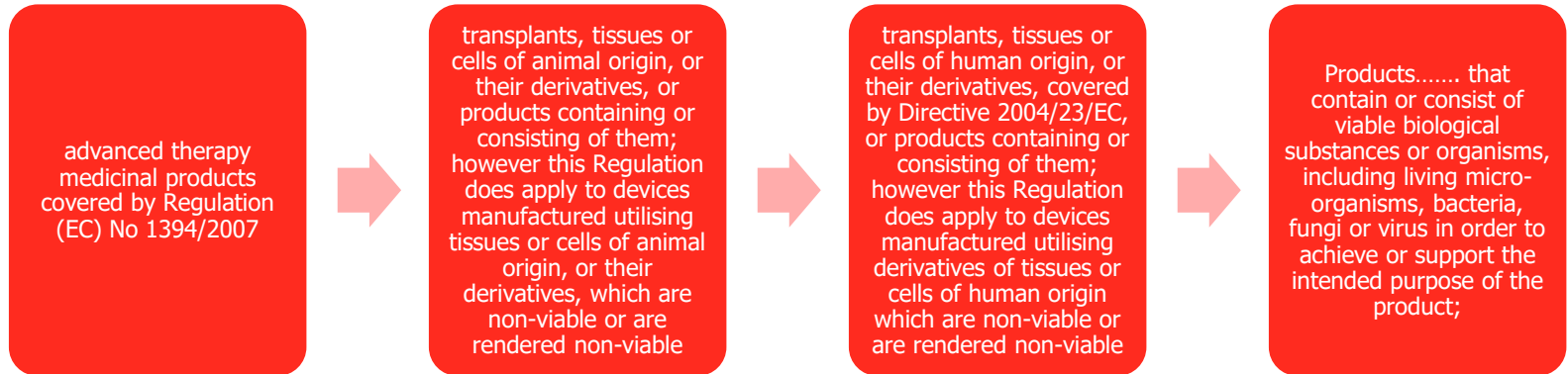
# Article 1 Scope

'Any device which, when placed on the market or put into service, incorporates, as an integral part, non-viable tissues or cells of human origin or their derivatives that have an action ancillary to that of the device shall be assessed and authorised in accordance with this Regulation. In that case, the provisions for donation, procurement and testing laid down in Directive 2004/23/EC shall apply.

However, if the action of those tissues or cells or their derivatives is principal and not ancillary to that of the device and the product is not governed by Regulation (EC) No 1394/2007, the product shall be governed by Directive 2004/23/EC. In that case, the relevant general safety and performance requirements set out in Annex I to this Regulation shall apply as far as the safety and performance of the device part are concerned.

# Article 1, Exclusions

## This regulation does not apply to:





## Conformity Assessment Process

devices manufactured utilising derivatives  
of tissues or cells of human origin which  
are non-viable or are rendered non-viable

## Annex IX, 5.3.1: Tissues or cells of human origin or their derivatives

the notified body shall, prior to issuing an EU technical documentation assessment certificate, seek a scientific opinion from one of the competent authorities designated by the Member States in accordance with Directive 2004/23/EC ('human tissues and cells competent authority') on the aspects relating to the donation, procurement and testing of tissues or cells of human origin or their derivatives. The notified body shall submit a summary of the preliminary conformity assessment which provides, among other things, information about the non-viability of the human tissues or cells in question, their donation, procurement and testing and the risk or benefit of the incorporation of the tissues or cells of human origin or their derivatives into the device.



# Annex IX, 5.3.1: Tissues or cells of human origin or their derivatives

## Notified Body Assessment



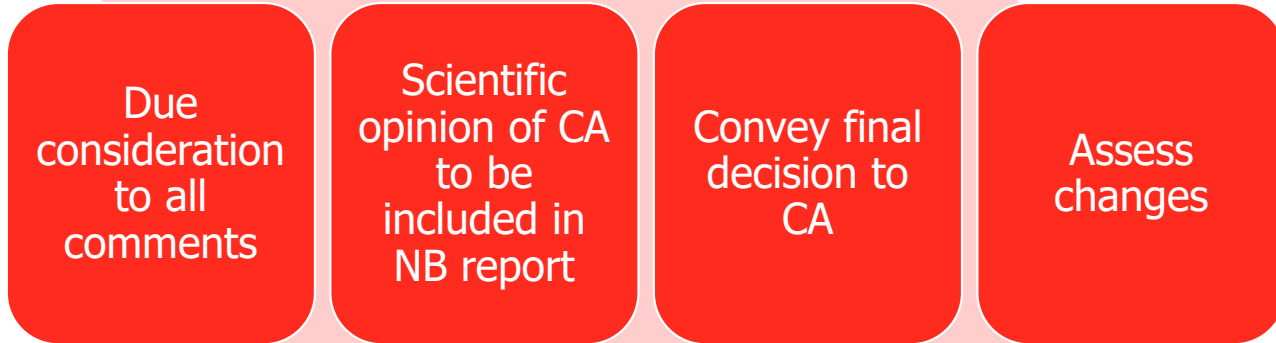
# Annex IX, 5.3.1: Tissues or cells of human origin or their derivatives

## Notified Body Assessment



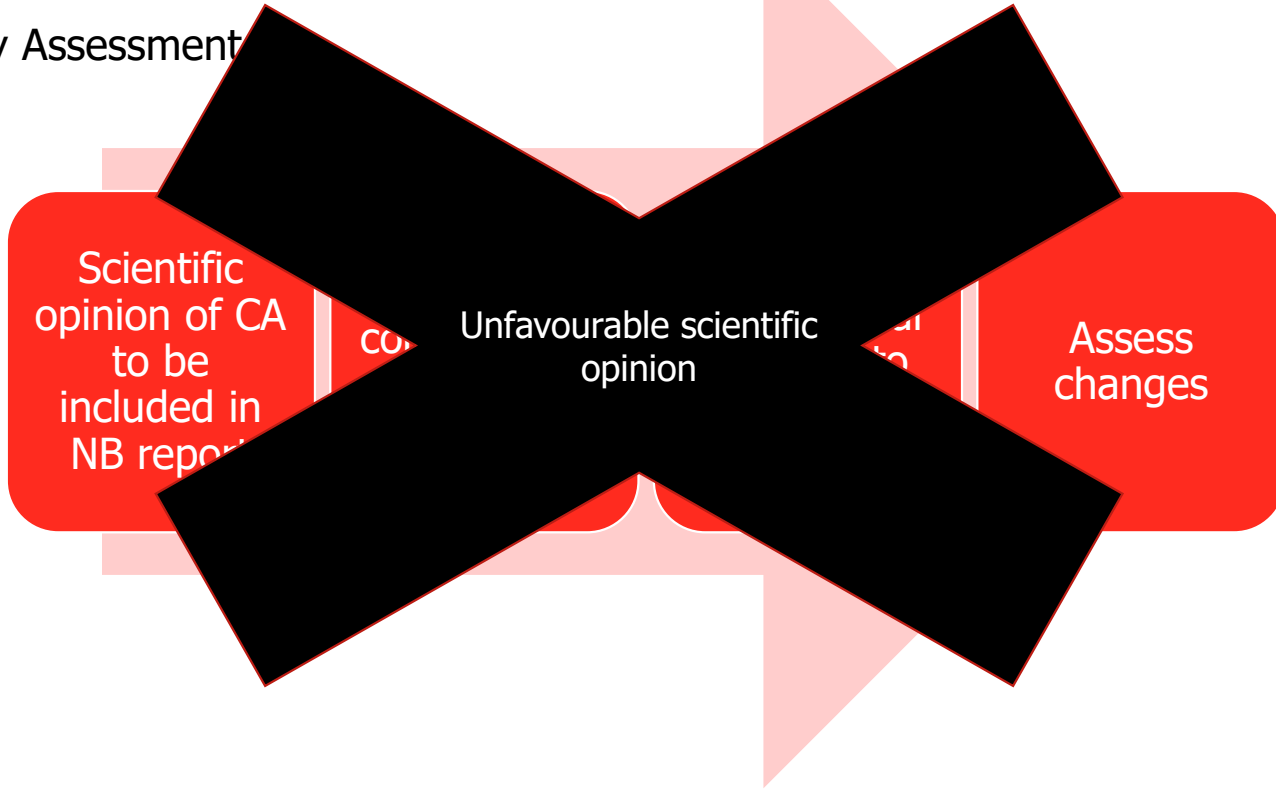
# Annex IX, 5.3.1: Tissues or cells of human origin or their derivatives

## Notified Body Assessment



# Annex IX, 5.3.1: Tissues or cells of human origin or their derivatives

Notified Body Assessment



## Annex IX, 5.3.1: Tissues or cells of human origin or their derivatives

**Changes [5.3.1 (d)]** Before any change is made with respect to non-viable tissues or cells of human origin or their derivatives incorporated in a device, in particular relating to their donation, testing or procurement,

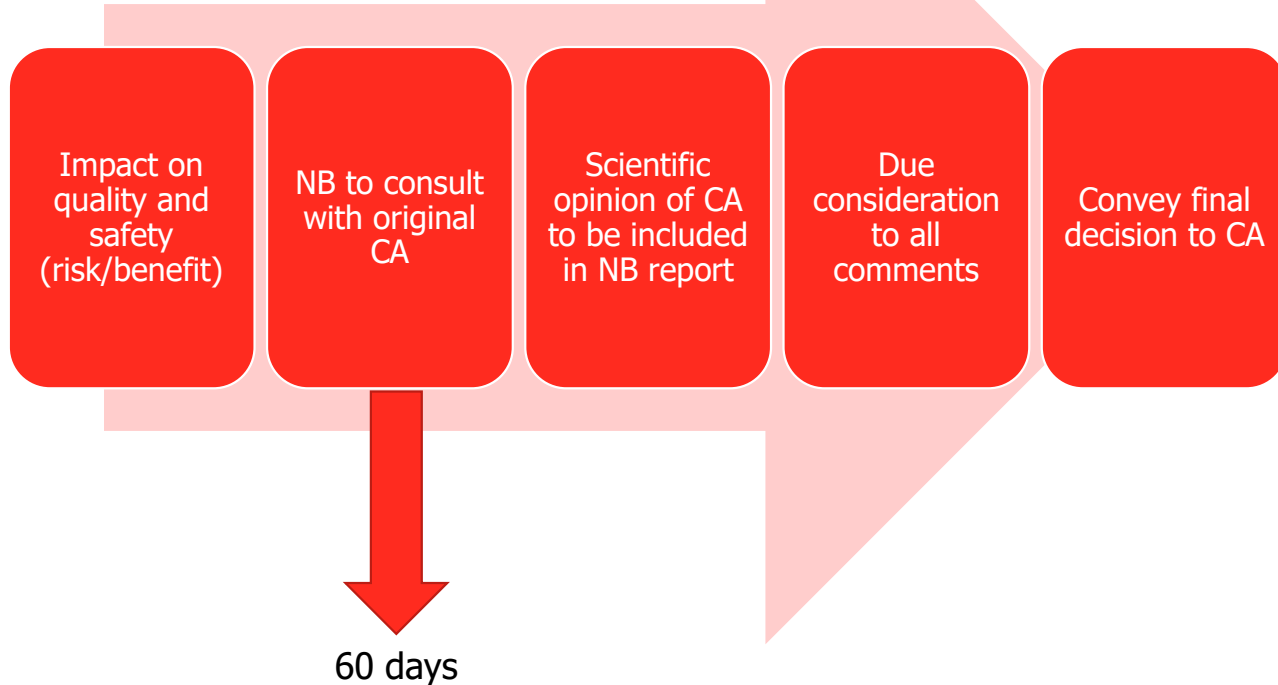
Other changes?

- Intended use
- Change to processing that could impact viral safety

**Manufacturer to inform Notified Body prior to implementation**

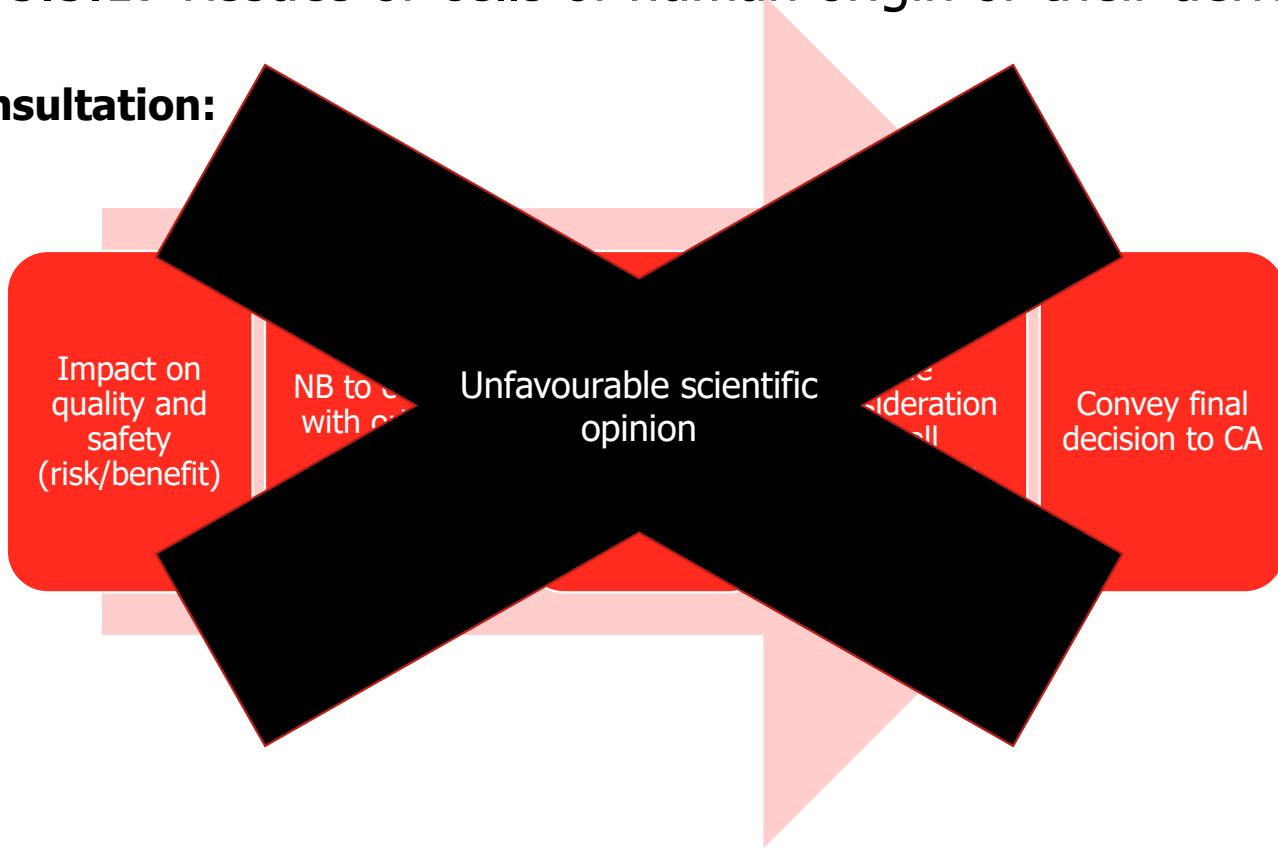
# Annex IX, 5.3.1: Tissues or cells of human origin or their derivatives

## Change Consultation:



# Annex IX, 5.3.1: Tissues or cells of human origin or their derivatives

## Change Consultation:





## Conformity Assessment Process

devices manufactured utilising animal tissue  
which is rendered non-viable or utilising non-  
viable products derived from animal tissue

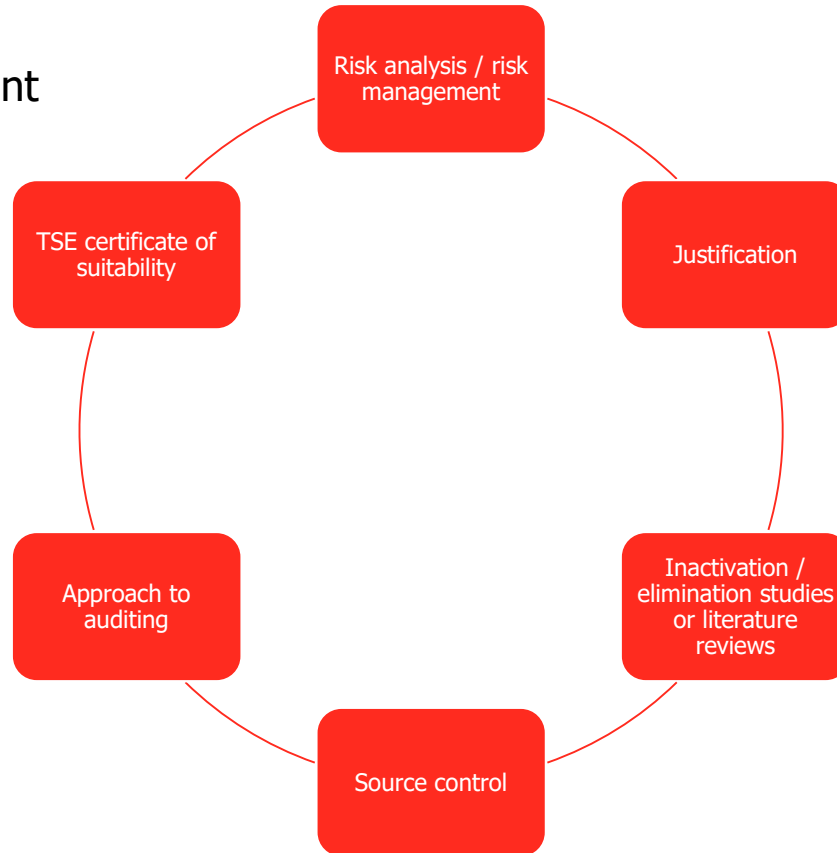


## Annex IX, 5.3.2: Tissues or cells of animal origin or their derivatives

In the case of devices manufactured utilising animal tissue which is rendered non-viable or utilising non-viable products derived from animal tissue, as referred to in Regulation (EU) No 722/2012, the notified body shall apply the relevant requirements laid down in that Regulation.

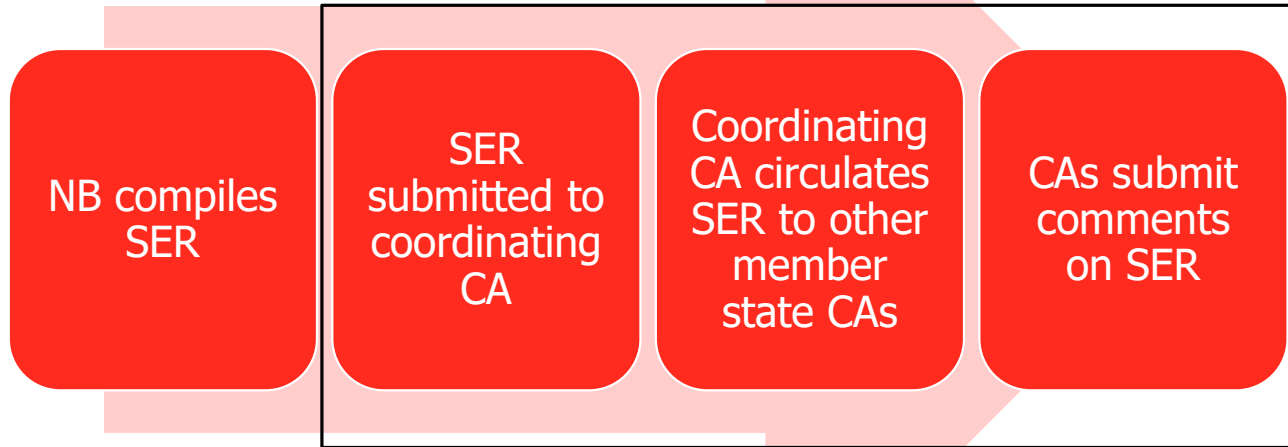
# Annex IX, 5.3.2: Tissues or cells of animal origin or their derivatives

## Notified Body Assessment



# Annex IX, 5.3.2: Tissues or cells of animal origin or their derivatives

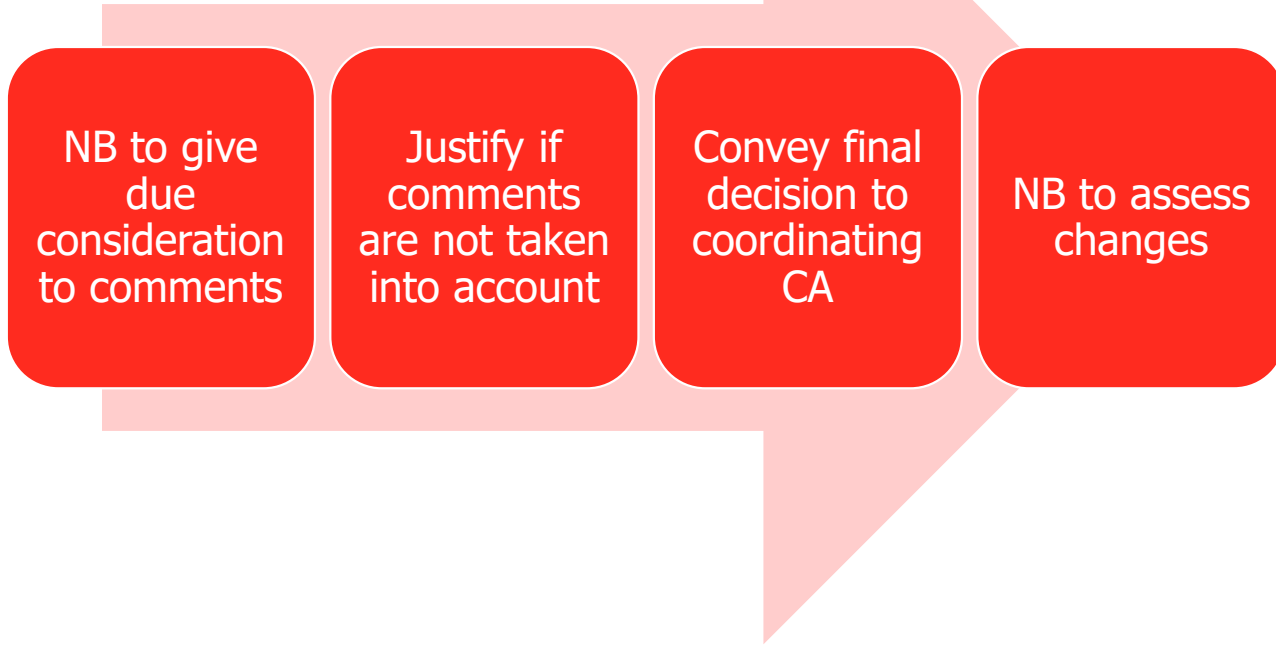
Notified Body Assessment  
722/2012 Consultation



4 weeks (EDQM) / 12 weeks (no EDQM)

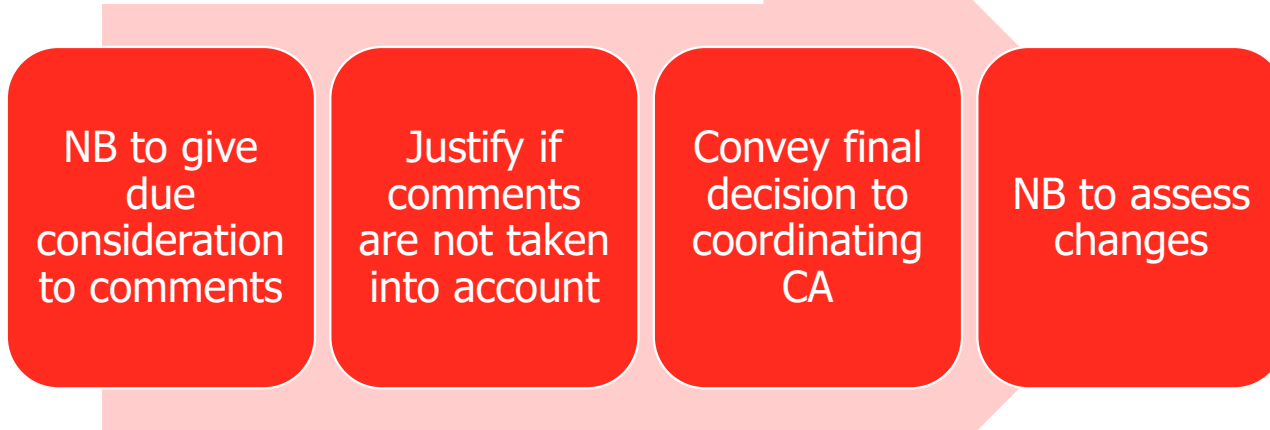
# Annex IX, 5.3.2: Tissues or cells of animal origin or their derivatives

Notified Body Assessment  
722/2012 Consultation



# Annex IX, 5.3.2: Tissues or cells of animal origin or their derivatives

Notified Body Assessment  
722/2012 Consultation



The manufacturer shall collect, evaluate and submit to the notified body information regarding changes with regard to the animal tissue or derivatives used for the device or with regard to the TSE risk in relation to the device. Where such information leads to an increase of the overall TSE risk, the provisions of paragraphs 1-6 are applicable

A thick teal arc curves across the top and right side of the slide, starting from the left edge and ending near the bottom right corner.

Devices composed  
on substances or  
combinations of  
substances

# Classification

## MDR Rule 21

Devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body are classified as:

- class III if they, or their products of metabolism, are systemically absorbed by the human body in order to achieve the intended purpose;
- class III if they achieve their intended purpose in the stomach or lower gastrointestinal tract and they, or their products of metabolism, are systemically absorbed by the human body;
- class IIa if they are applied to the skin or if they are applied in the nasal or oral cavity as far as the pharynx, and achieve their intended purpose on those cavities; and
- class IIb in all other cases.

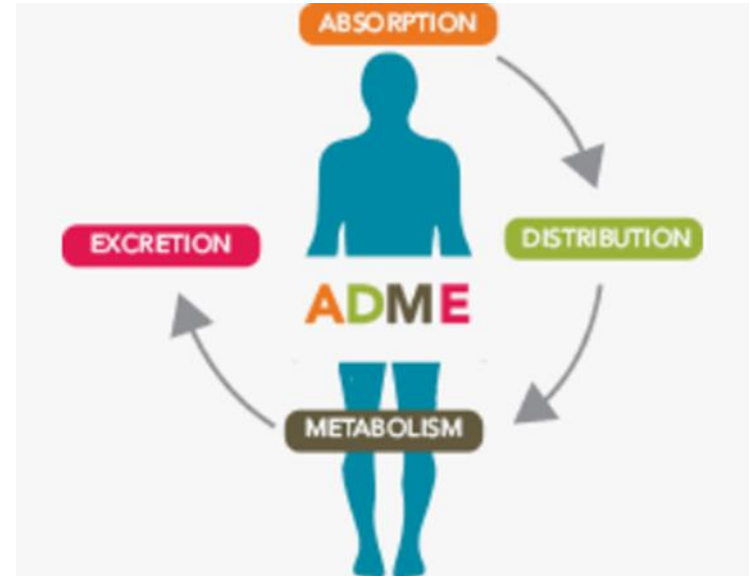
## Annex IX, 5.4: Procedure in the case of devices that are composed of substances or of combinations of substances that are absorbed by or locally dispersed in the human body

- (a) The quality and safety of devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by, or locally dispersed in, the human body, shall be verified where applicable and only in respect of the requirements not covered by this Regulation, in accordance with the relevant requirements laid down in Annex I to Directive 2001/83/EC for the evaluation of absorption, distribution, metabolism, excretion, local tolerance, toxicity, interaction with other devices, medicinal products or other substances and potential for adverse reactions.
- (b) In addition, for devices, or their products of metabolism, that are systemically absorbed by the human body in order to achieve their intended purpose, the notified body shall seek a scientific opinion from one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC or from the EMA, either of which to be referred to in this Section as 'the medicinal products authority consulted' depending on which has been consulted under this point, on the compliance of the device with the relevant requirements laid down in Annex I to Directive 2001/83/EC.
- (c) The opinion of the medicinal products authority consulted shall be drawn up within 150 days of receipt of all the necessary documentation.
- (d) The scientific opinion of the medicinal products authority consulted, and any possible update, shall be included in the documentation of the notified body concerning the device. The notified body shall give due consideration to the views expressed in the scientific opinion when making its decision and shall convey its final decision to the medicinal products authority consulted.



# Rule 21

- Devices that are composed of **substances** or of **combinations of substances** that are intended to be introduced into the human body via a body orifice or applied to the skin and that are **absorbed by or locally dispersed** in the human body
- Annex I 10.1 and 12.2
- Annex II 6.2 (c) for documentation
- Annex IX 5.4
- Directs us to **2001/83/EC**
- Scientific opinion from Competent Authority or EMA
  - If systemically absorbed in order to achieve purpose
  - 150 day process.



# Documentation Requirements



- **Detailed information**, including test design, complete test or study protocols, methods of data analysis, and data summaries and test conclusions regarding
- Absorption, distribution, metabolism and excretion
- Possible interactions of those substances, or of their products of metabolism in the human body, with other devices, medicinal products or other substances, considering the target population, and its associated medical conditions
- Local tolerance
- Toxicity, including single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, as applicable depending on the level and nature of exposure to the device.
- In the absence of such studies, a justification shall be provided.



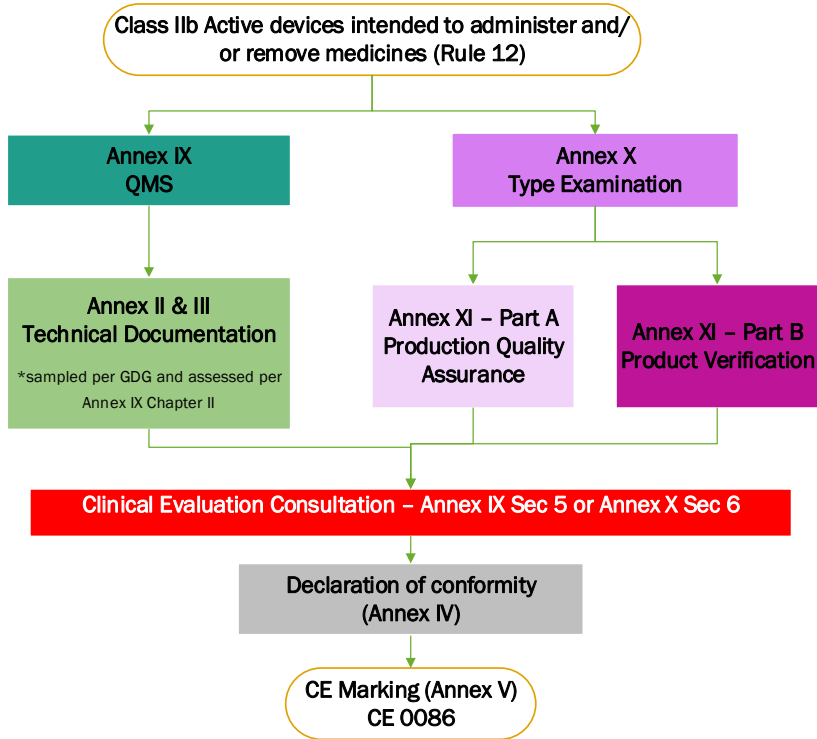
Class IIb Active  
Devices Intended to  
Administer and / or  
Remove Medicines

# Classification

## Rule 12

All active devices intended to administer and/or remove medicinal products, body liquids or other substances to or from the body are classified as class IIa, unless this is done in a manner that is potentially hazardous, taking account of the nature of the substances involved, of the part of the body concerned and of the mode of application in which case they are classified as class IIb.

# Art 52(4) + Art 54 – Class IIb Active devices intended to administer and/or remove medicines (rule 12)



**MDD comparison:**

- Addition of scrutiny procedure for devices covered by Rule 12

## Annex 1, SPR 10.3 (requirements regarding design and manufacture)

Devices shall be designed and manufactured in such a way that they can be used safely with the materials and substances, including gases, with which they enter into contact during their intended use; if the devices are intended to administer medicinal products they shall be designed and manufactured in such a way as to be compatible with the medicinal products concerned in accordance with the provisions and restrictions governing those medicinal products and that the performance of both the medicinal products and of the devices is maintained in accordance with their respective indications and intended use.

A thick teal arc curves across the top and right side of the page, starting from the left edge and ending near the bottom right corner.

IVF / ART

# Classification

## **MDD Rule 3**

All non-invasive devices intended for modifying the biological or chemical composition of blood, other body liquids or other liquids intended for infusion into the body are in Class IIb, unless the treatment consists of filtration, centrifugation or exchanges of gas, heat, in which case they are in Class IIa.

## **MDR Rule 3**

All non-invasive devices intended for modifying the biological or chemical composition of human tissues or cells, blood, other body liquids or other liquids intended for implantation or administration into the body are classified as class IIb, unless the treatment for which the device is used consists of filtration, centrifugation or exchanges of gas, heat, in which case they are classified as class IIa.

All non-invasive devices consisting of a substance or a mixture of substances intended to be used *in vitro* in direct contact with human cells, tissues or organs taken from the human body or used *in vitro* with human embryos before their implantation or administration into the body are classified as class III.



**bsi.**

...making excellence a habit.™