Medical Devices Utilising Biological Tissue: MDR Requirements

Jennifer Durrant, Ph.D

Agenda

- MDD / AIMD Requirements
- What changes under the MDR?
- Classification
- Routes of Conformity
- Conformity Assessment Process
- Safety and Performance Requirements
- Labelling Requirements
- Clinical Evaluation, Clinical Investigation and Post Market Clinical Follow Up
- MDR Timelines

MDD / AIMD Requirements

Devices utilising non viable animal tissues or derivatives, including those for which a TSE risk is suspected

Background to Animal Tissue Regulation

The BSE Crisis (vCJD)

- Fatal disease, long incubation periods
- Lack of suitable test, resistance of proteins to sterilisation processes
- 177 cases in UK, 237 worldwide, 100% fatality (http://www.cjd.ed.ac.uk/data.html)

Risk of infection from transmissible agents such as:

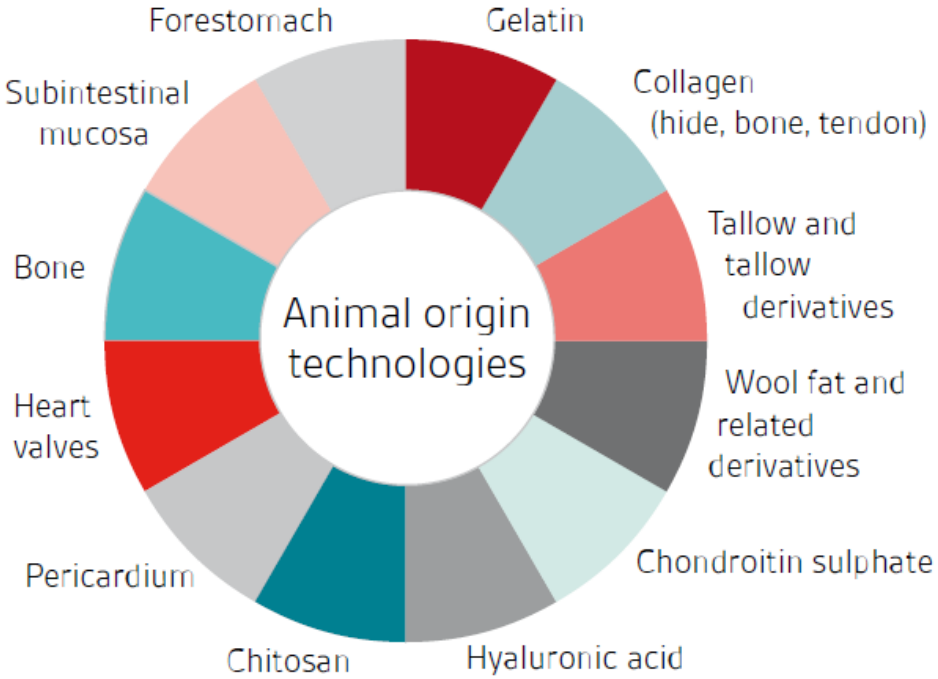
- Bacteria, moulds, yeasts, **viruses, agents causing TSE**
- Material responsible for undesired pyrogenic, immunological or toxicological reactions

What is an Animal?

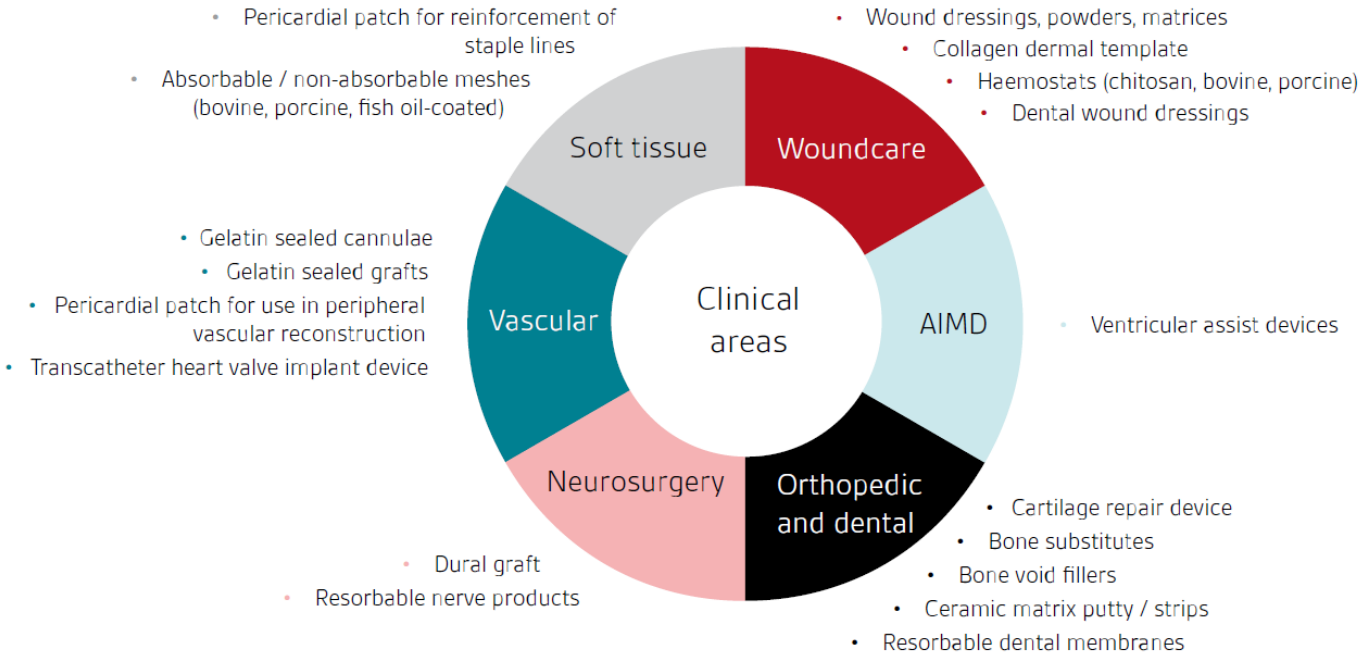
Any vertebrate or invertebrate [including amphibian, arthropod (e.g. crustacean), bird, coral, fish, reptile, mollusc and mammal] excluding humans

EN ISO 22442-1:2007 clause 3.1

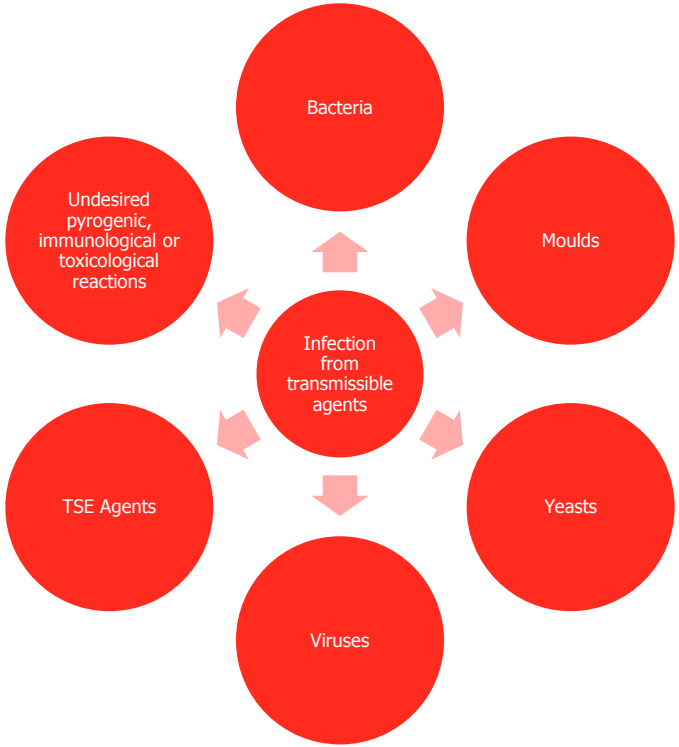
Examples of non viable animal tissues / derivatives



Device Technologies



What are the key risks?



How are the risks controlled?

Selection of source material for minimal contamination with viruses and/or TSE agents

Evidence to demonstrate the ability of a production process to remove or inactivate contamination with viruses and/or TSE agents

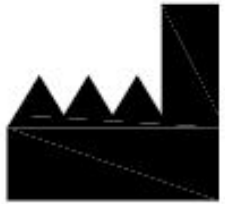
Legislation / Guidance

- EN ISO 22442
- MDD Rule 17
- Regulation 722/2012

Legislation / Guidance	Applicable to	Exclusions
EN ISO 22442 Parts 1-3	Any vertebrate or invertebrate [including amphibian, arthropod (e.g. crustacean), bird, coral, fish, reptile, mollusc and mammal] excluding humans	None (although special requirements are defined for some tissues)
Rule 17 (Class III)	All devices manufactured utilizing animal tissues or derivatives rendered non-viable	Milk, silk, wool, hair, lanolin, beeswax, tallow Devices that contact intact skin only
722/2012	Tissues originating from TSE-susceptible species (bovine, ovine, caprine, deer, elk, mink, cats)	Devices that do not contact the human body Devices that contact intact skin only

Directive / Regulation / Standards

Compliance must be demonstrated by the Legal Manufacturer, irrespective of outsourcing of supply or manufacture of animal tissue components or device



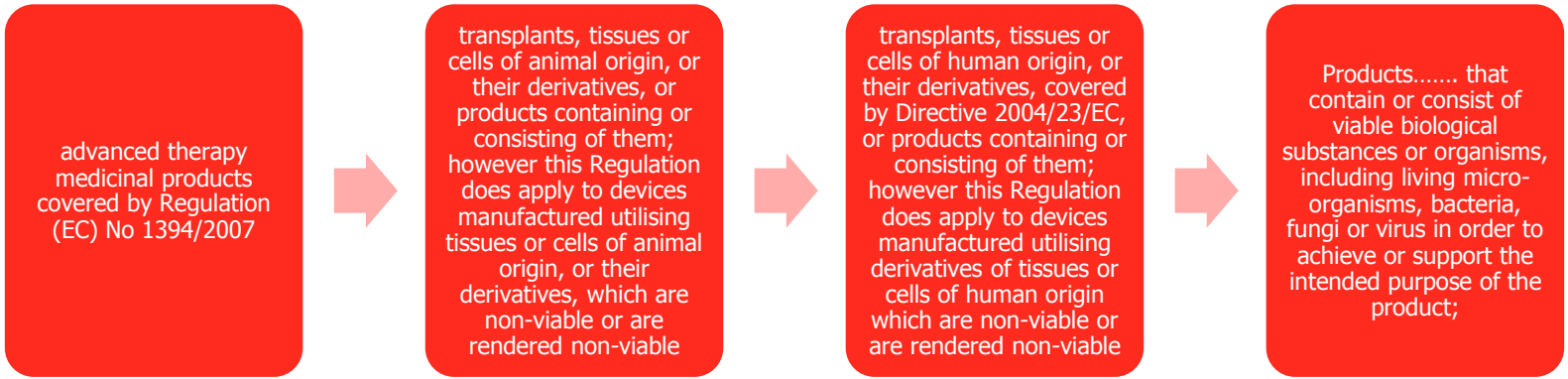
bsi.

What changes under the MDR?

Union legislation, in particular Regulation (EC) No 1394/2007 of the European Parliament and of the Council (1) and Directive 2004/23/EC of the European Parliament and of the Council (2), is incomplete in respect of certain products manufactured utilising derivatives of tissues or cells of human origin that are non-viable or are rendered non-viable. Such products should come under the scope of this Regulation, provided they comply with the definition of a medical device or are covered by this Regulation.

Article 1, Exclusions

This regulation does not apply to:



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 2, Definitions

‘**’medical device’** means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

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

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

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

— providing information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations,

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

Article 2, Definitions

- "'non-viable' means having no potential for metabolism or multiplication;
- 'derivative' means a "non-cellular substance" extracted from human or animal tissue or cells through a manufacturing process. The final substance used for manufacturing of the device in this case shall not contain any cells or tissues;
  - (722/2012 - **'derivative'** means a material obtained from animal tissue through one or more treatments, transformations or steps of processing)
- No definition included for 'tissue'
  - (722/2012 - **'tissue'** means an organisation of cells, extra-cellular constituents or both)

bsi.

Devices manufactured utilising non viable human tissues or cells, or their derivatives

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

Scope:

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.

Exclusions

transplants, tissues or cells of human origin, or their derivatives, covered by Directive 2004/23/EC, or products containing or consisting of them; however this Regulation does apply to devices manufactured utilising derivatives of tissues or cells of human origin which are non-viable or are rendered non-viable

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 in class III

Examples of non viable human tissues

- Decellularised human dermis
- Allograft tendons
- Demineralised bone
- Cartilage
- Pericardium
- Acellular cornea
- Fascia lata
- Heart valves

Classification

Classification Criteria (Annex IX, 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.

Classification Criteria (Annex VII, MDR)

Rule 18

~~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.~~

All devices manufactured utilising tissues or cells of human or animal origin, or their derivatives, which are non-viable or rendered non-viable are in 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 that are intended to come into contact with intact skin only.

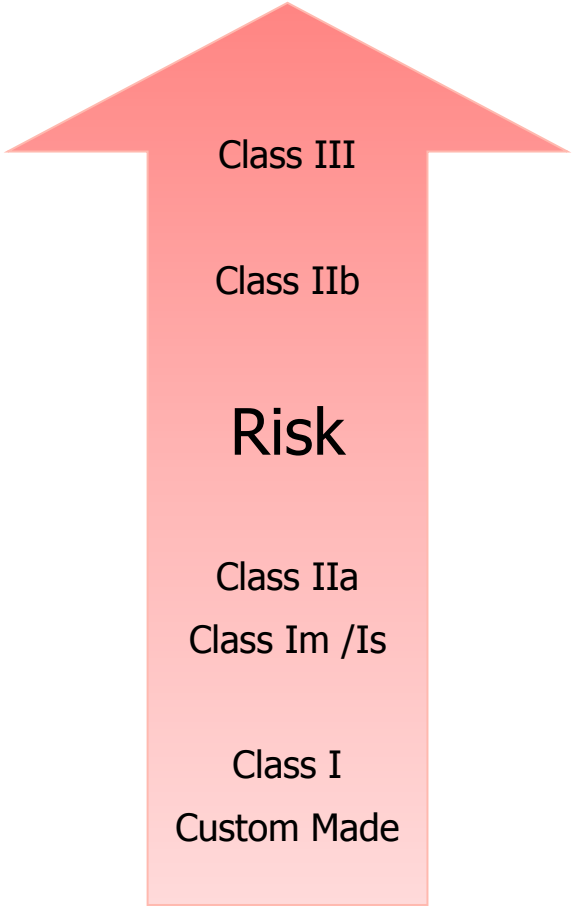
Routes of Conformity

Classification & Conformity Assessment – Directive

Competent Authority Assessment

Notified Body Conformity Assessment

Self-Certification



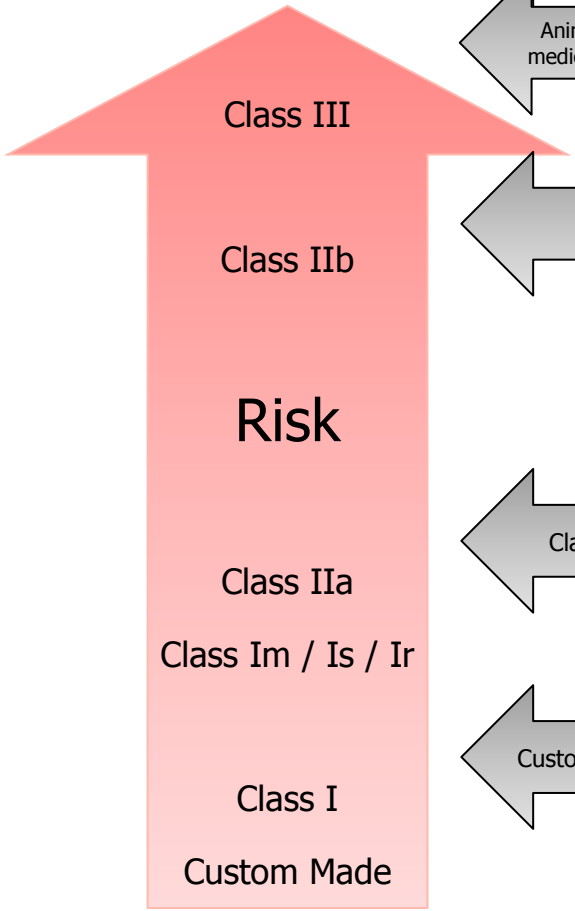
Classification & Conformity Assessment – Regulatio

Commission Assessment

Competent Authority Assessment

Notified Body Conformity Assessment

Self-Certification



Class III Implants & Class IIb active – delivering medicines

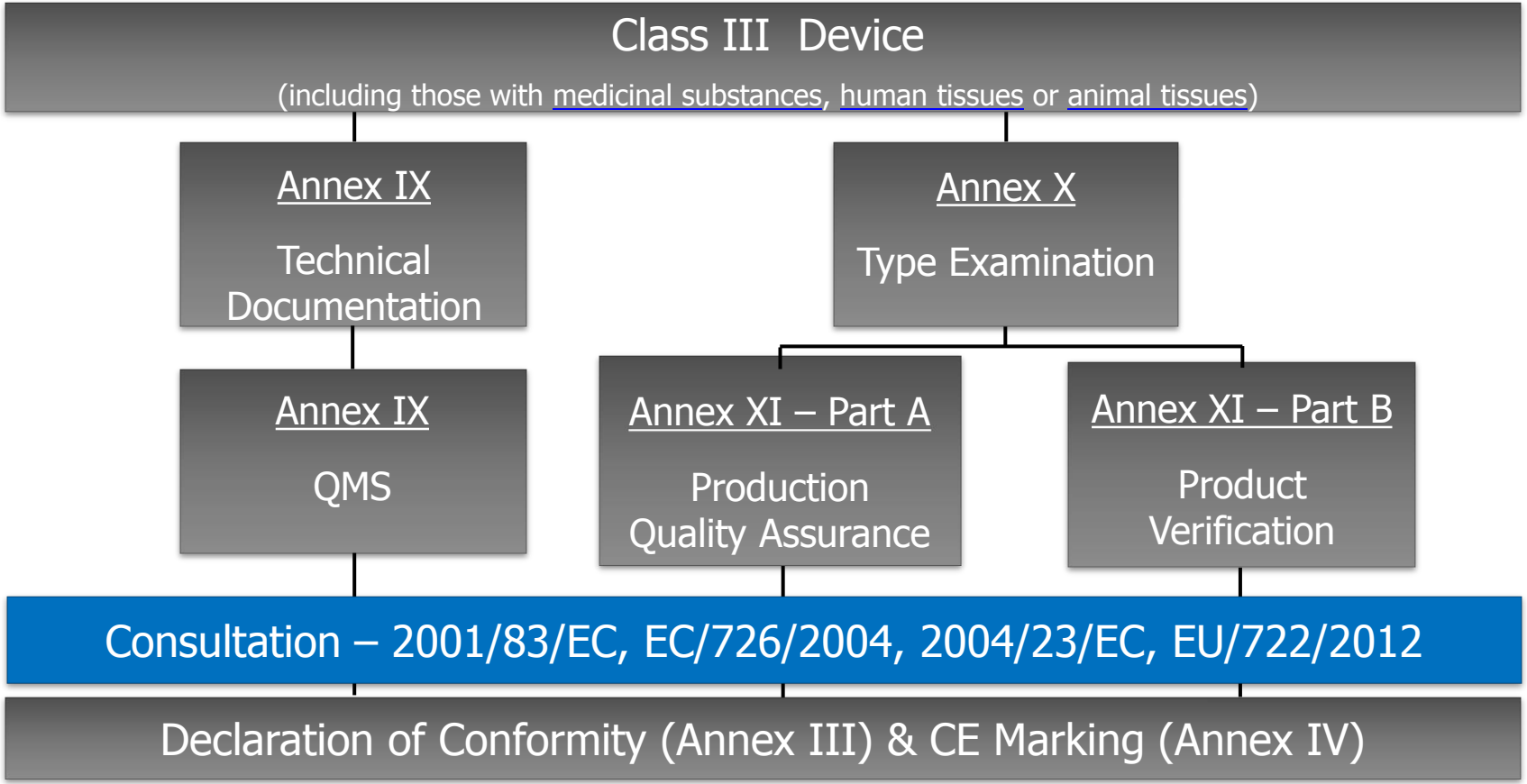
Animal tissues, human tissues, medicinal substances, absorbable

Class IIb Implants

Class IIa – more sampling

Custom Made Class III Implants

bsi.



bsi.

CE 0086 CE 0086

Article 42 Point 2

Conformity Assessment Process

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

Conformity Assessment Process – Annex IX, 5.3

Non viable human tissues / derivatives

Directive 2004/23/EC:

on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

Applies to:

- devices manufactured utilising derivatives of tissues or cells of human origin which are non-viable or are rendered non-viable
- devices that incorporate, as an integral part, tissues or cells of human origin, or their derivatives, covered by Directive 2004/23/EC, that have an action ancillary to that of the device

Non viable animal tissues / derivatives (TSE susceptible)

Regulation 722/2012:

concerning particular requirements as regards the requirements laid down in Council Directives 90/385/EEC and 93/42/EEC with respect to active implantable medical devices and medical devices manufactured utilising tissues of animal origin

Applies to:

- 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

(animal tissues, as well as their derivatives, originating from bovine, ovine and caprine species, deer, elk, mink and cats)

Non viable animal tissues / derivatives (non-TSE susceptible)

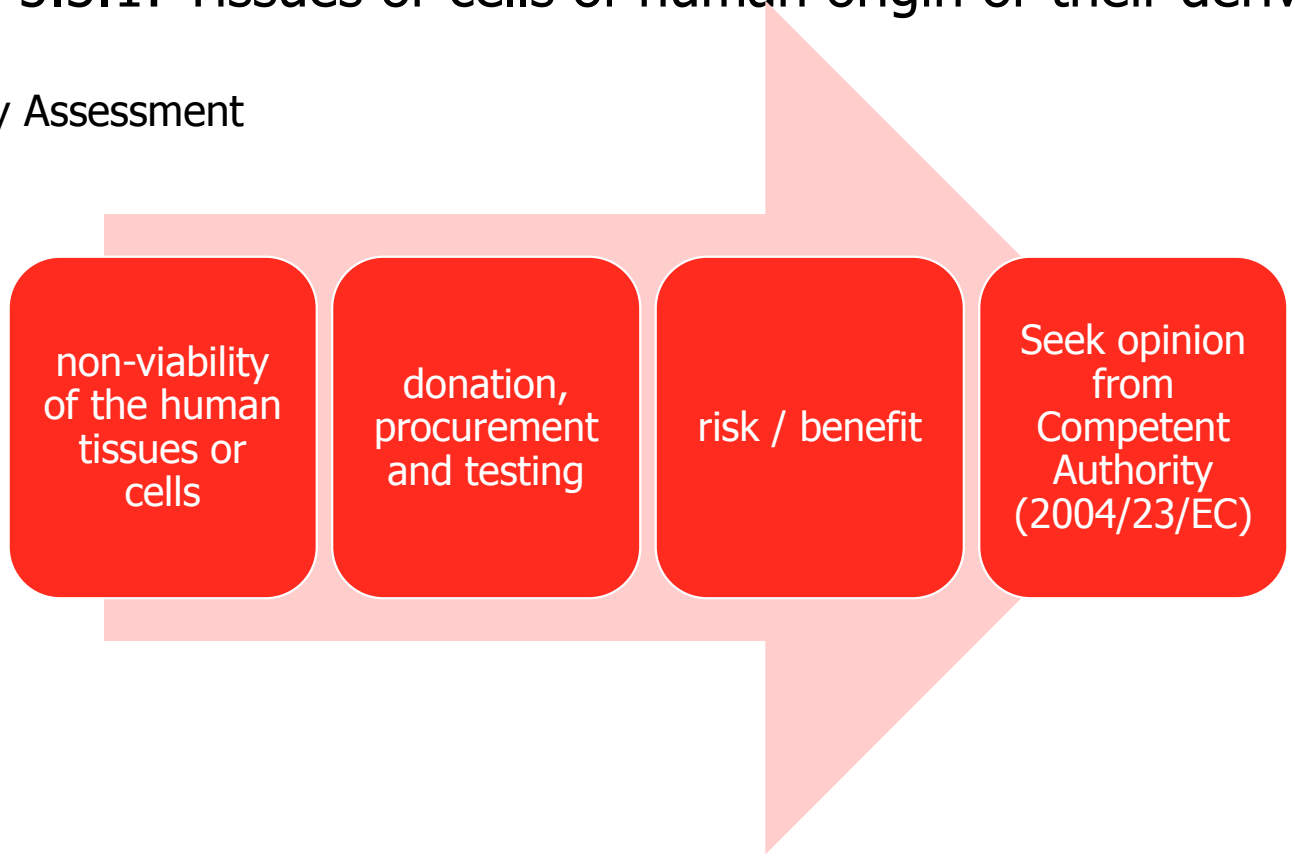
- No consultation required

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.

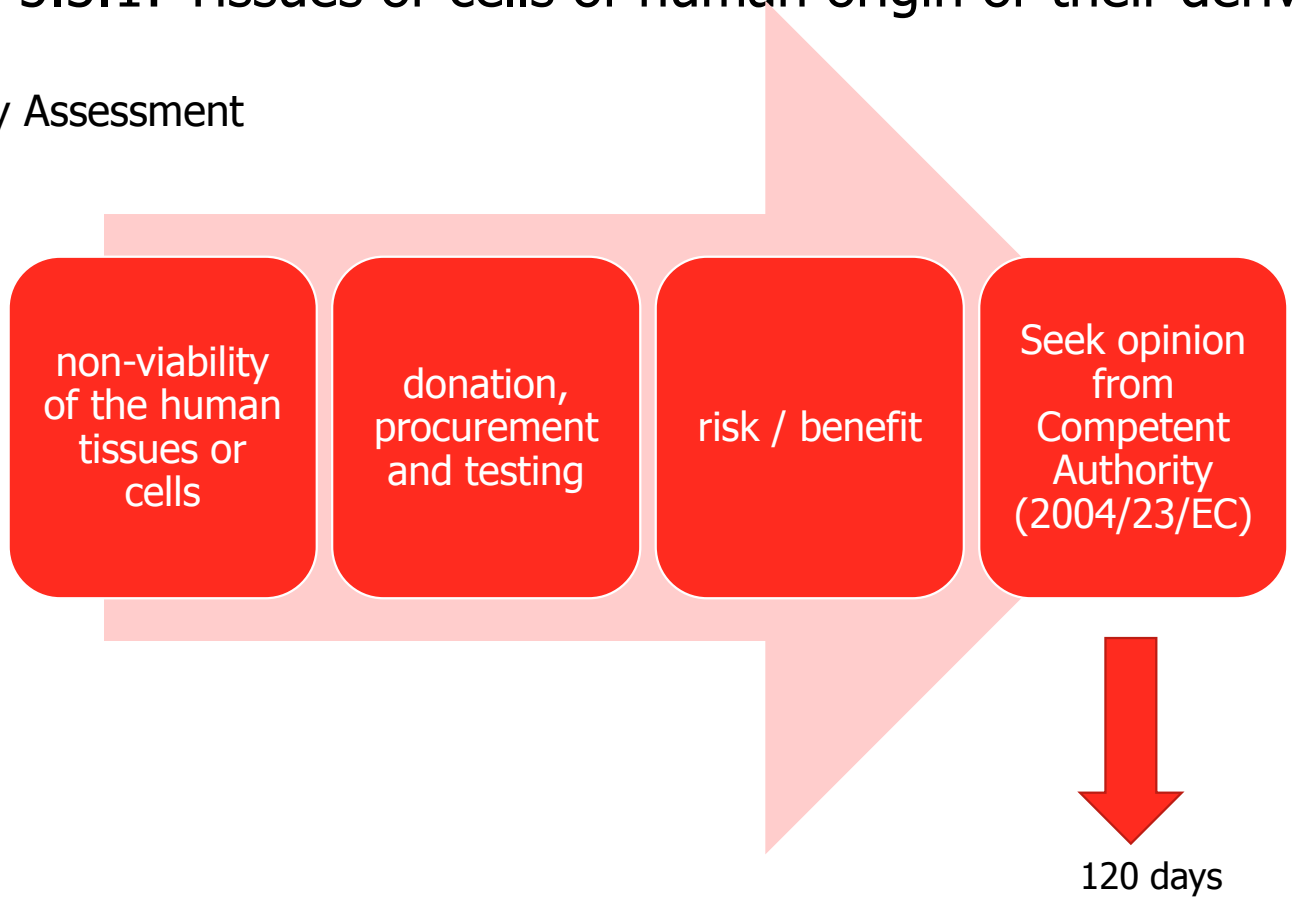
Annex IX, 5.3.1: Tissues or cells of human origin or their derivatives

Notified Body Assessment



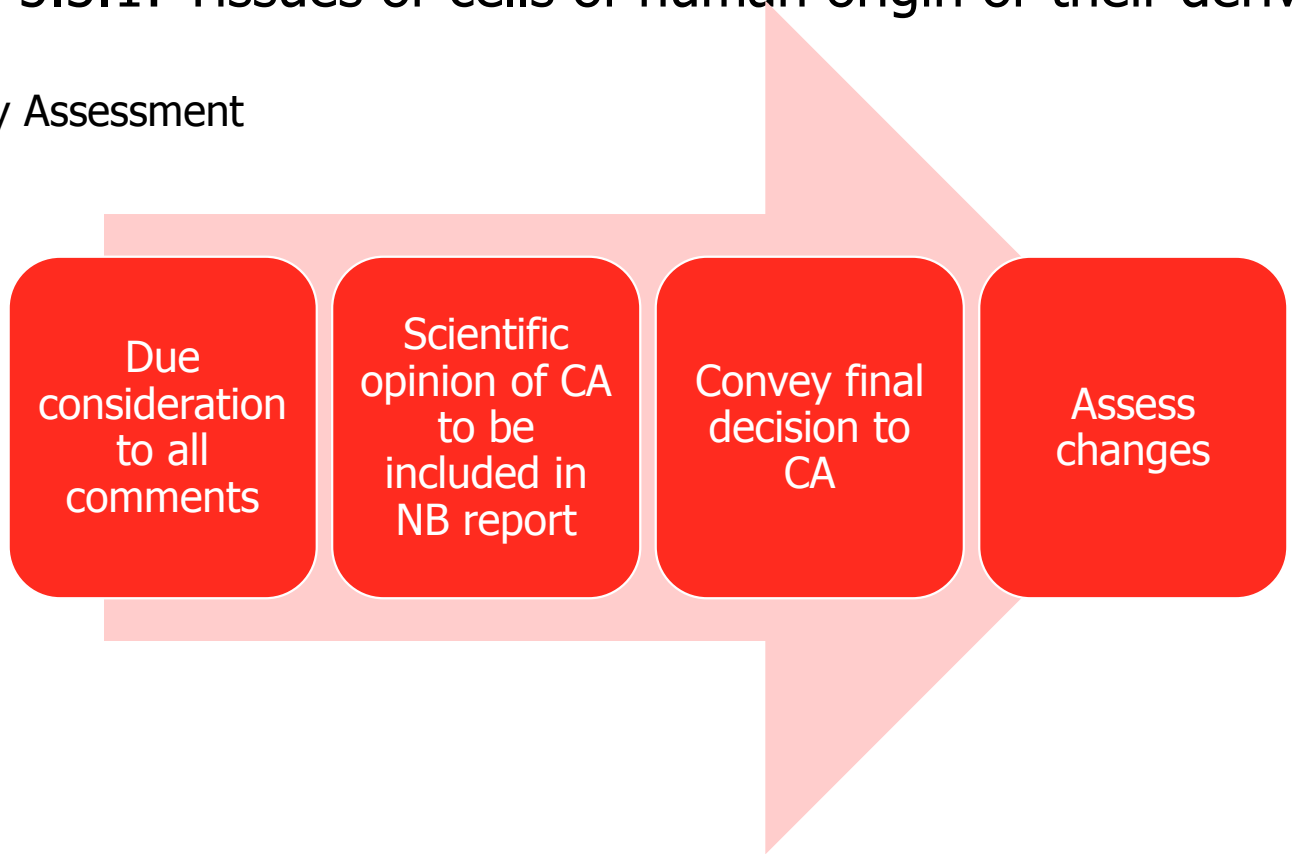
Annex IX, 5.3.1: Tissues or cells of human origin or their derivatives

Notified Body Assessment



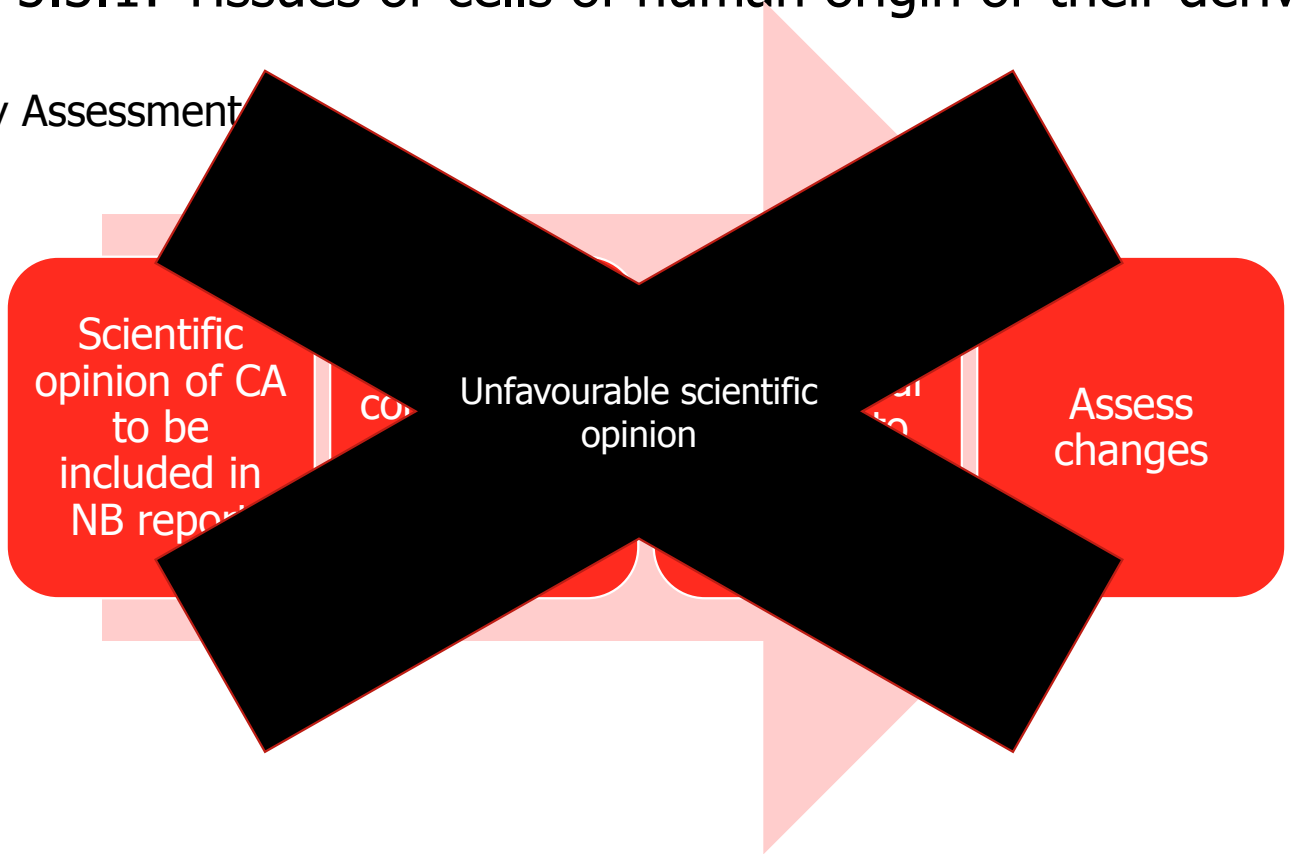
Annex IX, 5.3.1: Tissues or cells of human origin or their derivatives

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,

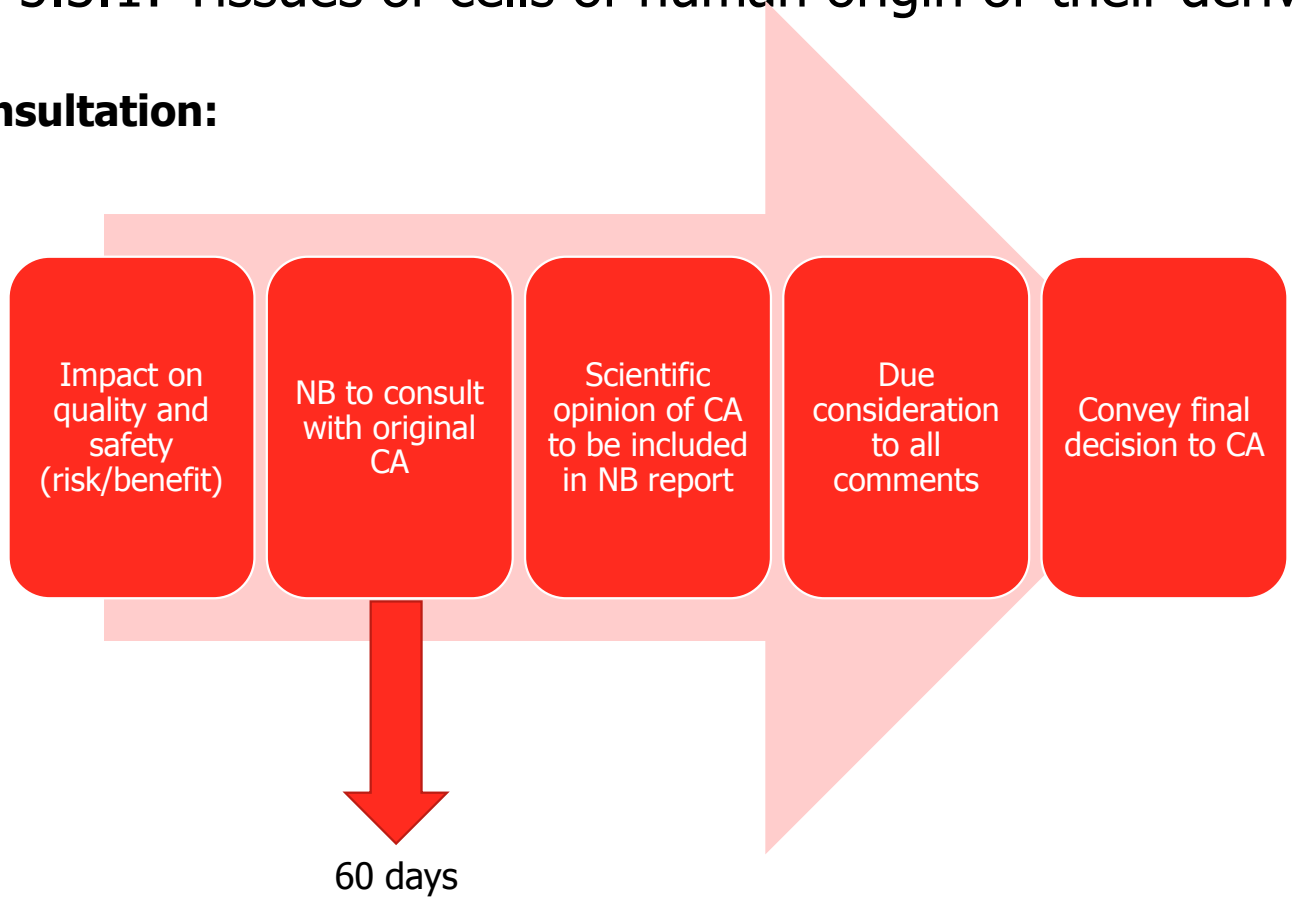
Other changes?

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

Manufacturer to inform Notified Body prior to implementation

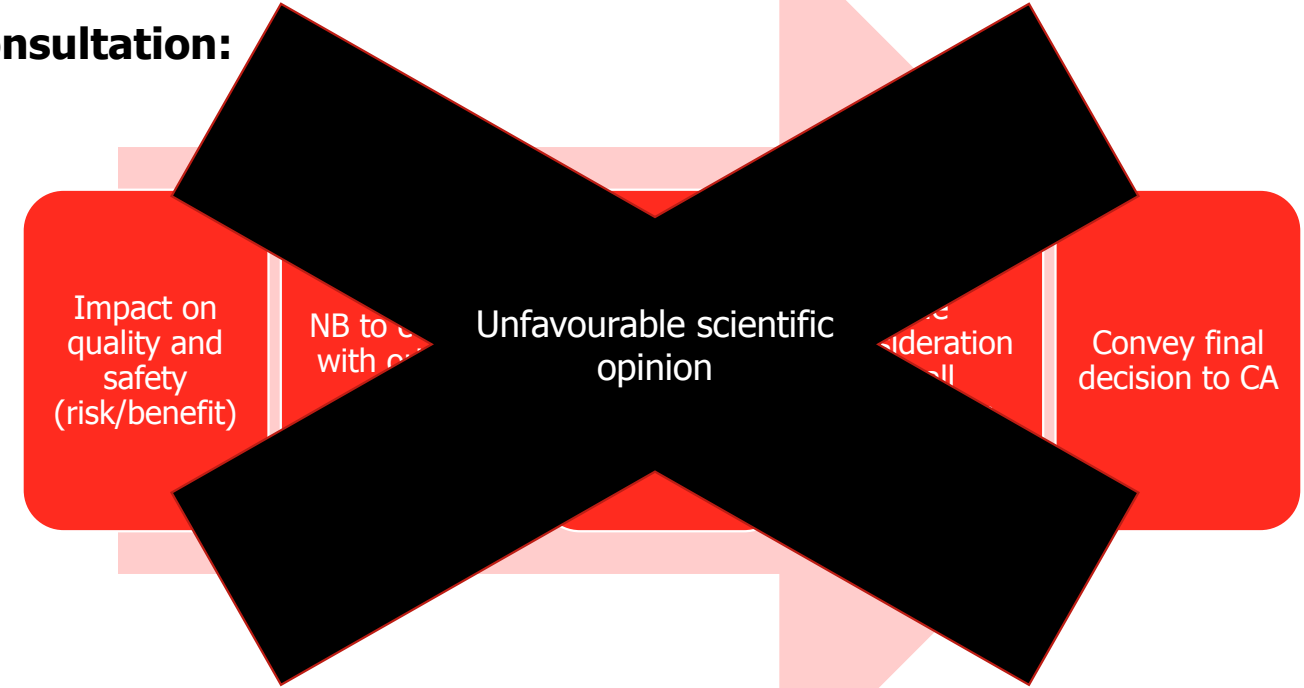
Annex IX, 5.3.1: Tissues or cells of human origin or their derivatives

Change Consultation:



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

Change Consultation:



Conformity Assessment Process

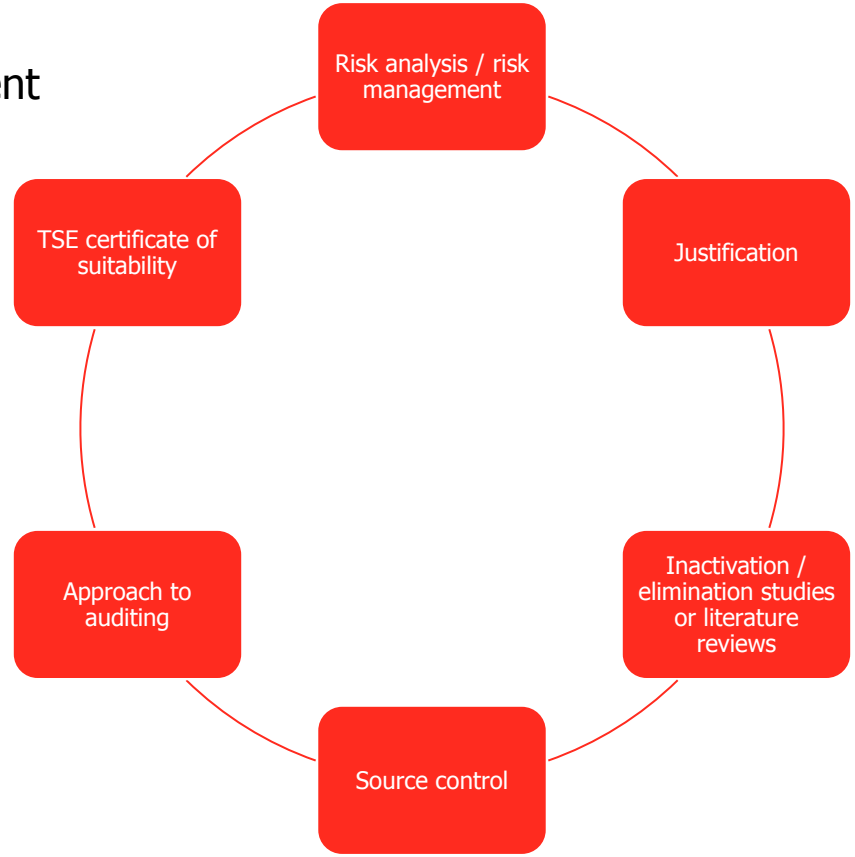
devices manufactured utilising animal tissue which is rendered non-viable or utilising non-viable products derived from animal tissue

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

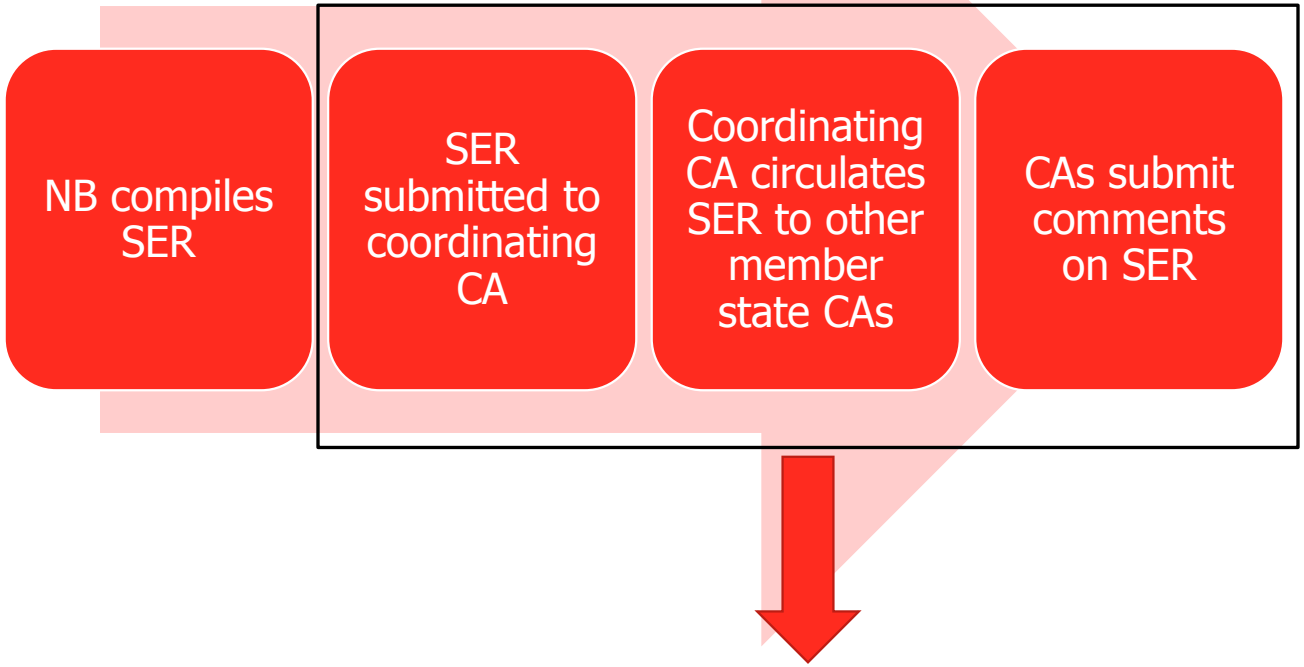
Notified Body Assessment



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

Notified Body Assessment

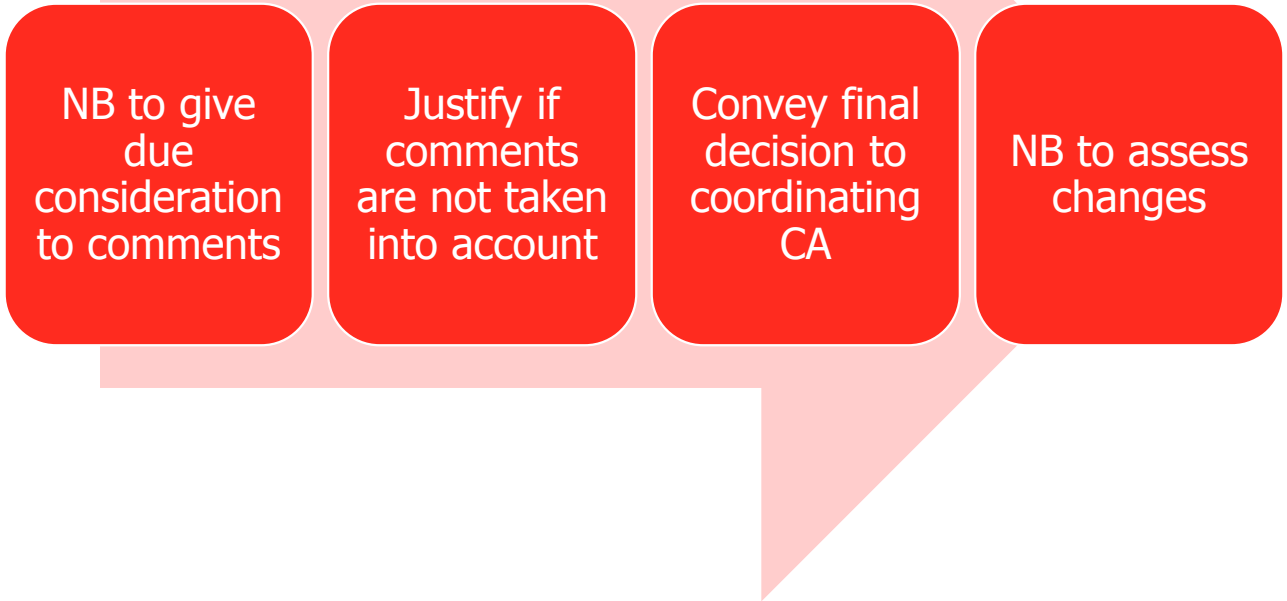
722/2012 Consultation



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

Notified Body Assessment

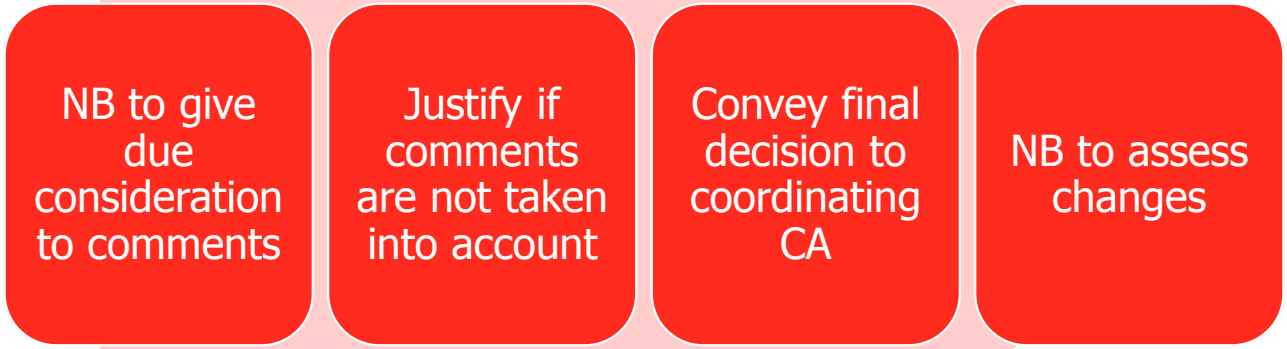
722/2012 Consultation



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

Safety and Performance Requirements

Annex I

MDD 93/42/EEC

Essential Requirement #8.2

Tissues of animal origin must originate from animals that have been subjected to veterinary controls and surveillance adapted to the intended use of the tissues.

Notified bodies shall retain information on the geographical origin of the animals.

Processing, preservation, testing and handling of tissues, cells and substances of animal origin must be carried out so as to provide optimal security. In particular safety with regard to viruses and other transmissible agents must be addressed by implementation of validated methods of elimination or viral inactivation in the course of the manufacturing process.

SPR 13.1 For devices manufactured utilising derivatives of tissues or cells of human origin which are non-viable or are rendered non-viable covered by this Regulation in accordance with point (g) of Article 1(6), the following shall apply:

(a) donation, procurement and testing of the tissues and cells shall be done in accordance with Directive 2004/23/EC;

(b) processing, preservation and any other handling of those tissues and cells or their derivatives shall be carried out so as to provide safety for patients, users and, where applicable, other persons. In particular, safety with regard to viruses and other transmissible agents shall be addressed by appropriate methods of sourcing and by implementation of validated methods of elimination or inactivation in the course of the manufacturing process;

(c) the traceability system for those devices shall be complementary and compatible with the traceability and data protection requirements laid down in Directive 2004/23/EC and in Directive 2002/98/EC.

SPR 13.1 For devices manufactured utilising derivatives of tissues or cells of human origin which are non-viable or are rendered non-viable covered by this Regulation in accordance with point (g) of Article 1(6), the following shall apply:

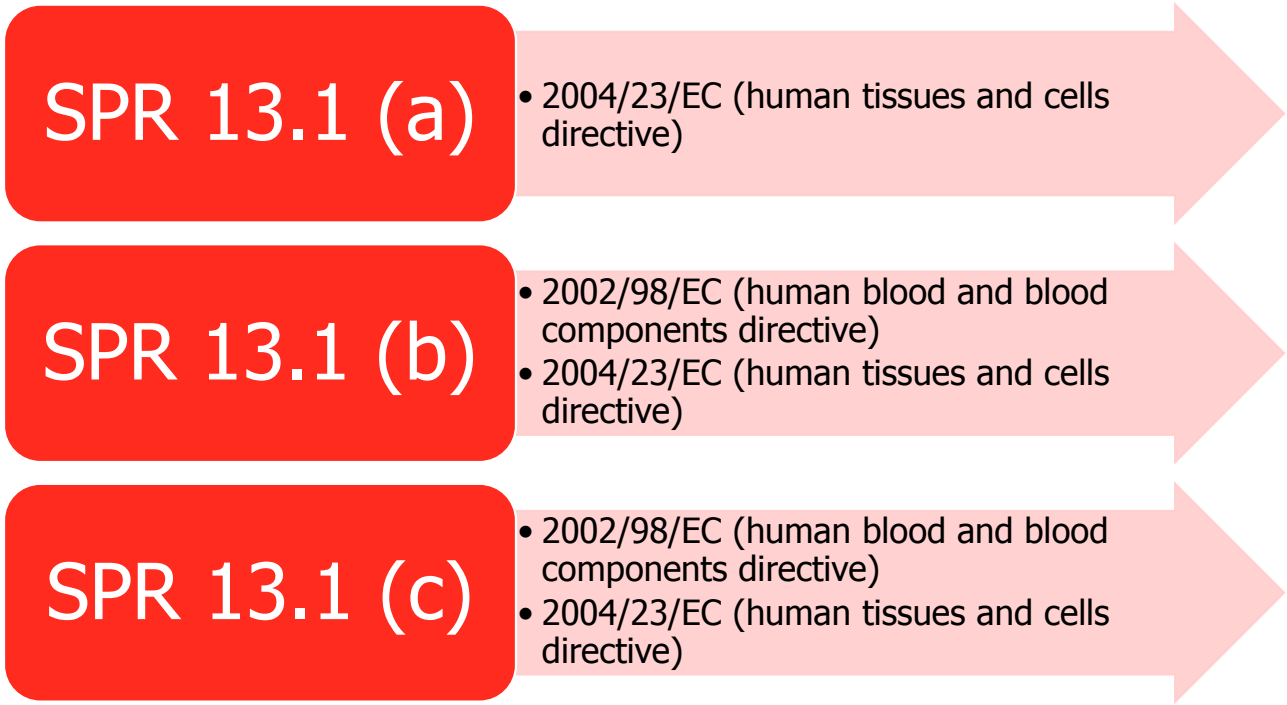
(a) donation, procure … cordance with Directive 2004/23

(b) processing, prese … heir derivatives shall be carried o… icable, other persons. In partic… ents shall be addressed by app… ated methods of elimination or ina…

(c) the traceability sy… ole with the traceability and d… C and in Directive 2002/98/EC.

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

SPR 13.1 For devices manufactured utilising derivatives of tissues or cells of human origin which are non-viable or are rendered non-viable covered by this Regulation in accordance with point (g) of Article 1(6), the following shall apply:



SPR 13.2 For devices manufactured utilising tissues or cells of animal origin, or their derivatives, which are non-viable or rendered non-viable the following shall apply:

(a) where feasible taking into account the animal species, tissues and cells of animal origin, or their derivatives, shall originate from animals that have been subjected to veterinary controls that are adapted to the intended use of the tissues. Information on the geographical origin of the animals shall be retained by manufacturers;

(b) sourcing, processing, preservation, testing and handling of tissues, cells and substances of animal origin, or their derivatives, shall be carried out so as to provide safety for patients, users and, where applicable, other persons. In particular safety with regard to viruses and other transmissible agents shall be addressed by implementation of validated methods of elimination or viral inactivation in the course of the manufacturing process, except when the use of such methods would lead to unacceptable degradation compromising the clinical benefit of the device;

(c) in the case of devices manufactured utilising tissues or cells of animal origin, or their derivatives, as referred to in Regulation (EU) No 722/2012 the particular requirements laid down in that Regulation shall apply.

SPR 13.2 For devices manufactured utilising tissues or cells of animal origin, or their derivatives, which are non-viable or rendered non-viable the following shall apply:

SPR 13.2 (a)

- EN ISO 22442-2 clause 5, annexes
- 722/2012 annex 1, 1.2.1-1.2.4
- EN ISO 22442-1 annex D

SPR 13.2 (b)

- EN ISO 22442-2 clauses 5-8, annexes
- EN ISO 22442-3 clauses 5-9, annexes
- 722/2012 annex 1, 1.2.4-1.2.5
- EN ISO 22442-1 annex D

SPR 13.2 (c)

- Commission Regulation (EU) No 722/2012

SPR 13.3

For devices manufactured utilising non-viable biological substances other than those referred to in Sections 13.1 and 13.2, the processing, preservation, testing and handling of those substances shall be carried out so as to provide safety for patients, users and, where applicable, other persons, including in the waste disposal chain. In particular, safety with regard to viruses and other transmissible agents shall be addressed by appropriate methods of sourcing and by implementation of validated methods of elimination or inactivation in the course of the manufacturing process.

Labelling Requirements

Safety and Performance Requirements

SPR 23.2

The label shall bear the following particulars:

(e) Where applicable, an indication that the device contains or incorporates,

- - tissues or cells, or their derivatives, of human origin, or
- - tissues or cells, or their derivatives, of animal origin as referred to in Commission Regulation (EU) No 722/2012.

SPR 23.4

The instructions for use shall contain the following particulars:

(s) Information that allows the user and/or patient to be informed and, where relevant, to brief the patient of any warnings, precautions, contra - indications, measures to be taken and limitations of use regarding the device. This information shall cover, where appropriate:

- if the device is intended to administer….. tissues or cells, or their derivatives, of human or animal origin or biological substances, any limitations or incompatibility in the choice of substances to be delivered;

SPR#4

Risk control measures adopted by manufacturers for the design and manufacture of the devices shall conform to safety principles, taking account of the generally acknowledged state of the art. To reduce risks, Manufacturers shall manage risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable.

In selecting the most appropriate solutions, manufacturers shall, in the following order of priority:

(a) eliminate or reduce risks as far as possible through safe design and manufacture;

(b) where appropriate, take adequate protection measures, including alarms if necessary, in relation to risks that cannot be eliminated; and

(c) provide information for safety (warnings/ precautions/ contraindications) and, where appropriate, training to users.

Manufacturers shall inform users of any residual risks.

Clinical Evaluation, Clinical Investigation and Post Market Clinical Follow Up

Annex XIV Clinical Evaluation and Post Market Clinical Follow Up

Clinical Evaluation

To plan, continuously conduct and document a clinical evaluation, a manufacturer shall:

(a) establish and update a clinical evaluation plan, which shall include at least:

- an indication how risk/benefit issues relating to specific components such as use of pharmaceutical, non-viable animal/human tissues are to be addressed;

Annex XV Clinical Investigations

Documentation regarding the application for clinical investigation

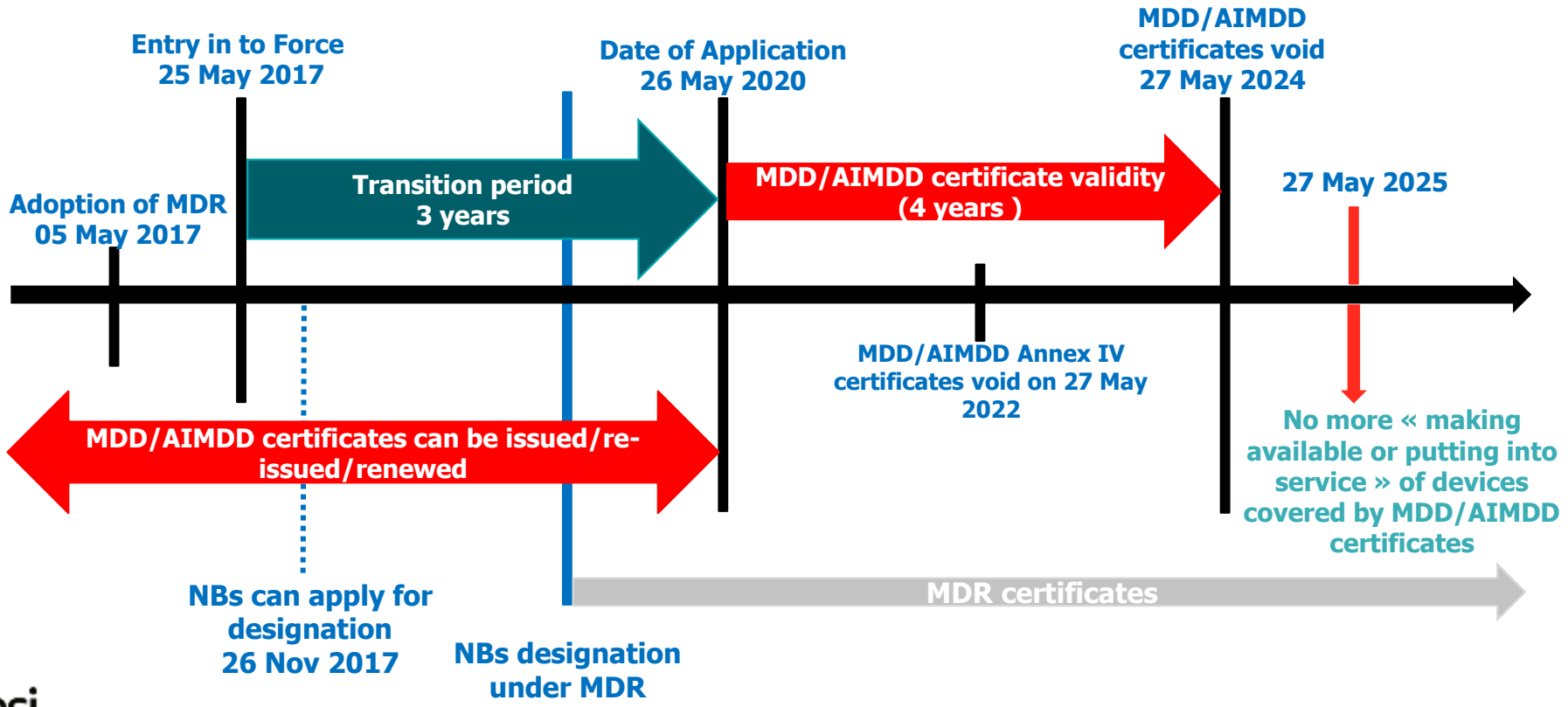
1.10. Information as to whether the device incorporates a medicinal substance, including a human blood or plasma derivative, or whether it is manufactured utilising non-viable tissues or cells of human or animal origin, or their derivatives.

Investigators Brochure

2.6. In the case of devices that incorporate a medicinal substance, including a human blood or plasma derivative, or devices manufactured utilising non-viable tissues or cells of human or animal origin, or their derivatives, detailed information on the medicinal substance or on the tissues or cells, and on the compliance with the relevant general safety and performance requirements and the specific risk management in relation to the substance or tissues, cells or their derivatives, as well as evidence of the added value of incorporation of these constituents to the clinical benefit and/or safety of the device.

MDR Timelines

MDR Transition (Article 120)



Where to find additional information?

- https://www.bsigroup.com/en-GB/medical-devices/our-services/MDR-Revision/
- https://www.bsigroup.com/en-GB/medical-devices/our-services/Regulatory-strategy-review/