BSI Medicines & Biologics

Dr Jennifer Durrant
Global Head, Medicinal & Biologics Team
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, etc.

**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

Richard Pearce
Operations Director CE

Teresa Perry
Global QMS Manager

Patrick Murphy
Global MDSAP Manager

Lou Stinson
Global Head Microbiology

Global QMS Certification Team

Erica Conway
Global Head *In Vitro* Diagnostics

Monisha Phillips
Global Head Orthopaedic and Dental

David Adams
Global Head Active Devices

Paul Risborough
Global Head AIMD

Maritza Carballo
Global Head Vascular

Haydar Jaafar
Global Head General Devices

Jennifer Durrant
Global Head Medicinal and Biologics
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

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Correct as of July 2018
Medicinal & Biologics Team Structure:

Global Head Medicinal & Biologics Team

Technical Team Manager
Peter Bowness

Technical Specialists (medicines, human blood, ingestibles)
Susanne Fornero, Jonathan Sutch, Arabe Ahmed

4 x Scheme Manager / Technical Specialists (animal tissue, human tissue, IVF, ART, organ preservation)
Chuck Thomas, Sebastien Francois, Fredric Hidesand, Henrik Persson
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
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 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

26 Nov 2017
NBs can apply for designation

26 May 2020
Date of application

MDD/AIMDD certificates can no longer be issued

MDR certificates valid

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
MDR Impact

Significant impact for clients who wish to place these products on the market
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.
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
- Metered dose inhaler (combined)
- Transdermal contraceptive patch
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:

1. Quotation processed & contract review
2. Technical documentation provided
3. BSI technical assessment
4. Responses & questions cycle
5. Closeout of questions based on technical specialist recommendation
6. Certificate decision (independent review)
7. Summary document / report issued to manufacturer
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)
| 2. | Risk reduction as far as possible | 11. | Infection & Microbial Contamination |
| 3. | **Risk Management** | 12. | Devices incorporating a medicinal product and devices composed of substances that are absorbed by or locally dispersed in the human body |
| 4. | Risk Control | 13. | Devices incorporating **materials of biological origin** |
| 5. | Risk of **Use Error** | 14. | Construction and **interaction with the environment** |
| 6. | Lifetime | 15. | Devices with a diagnostic or measuring function |
| 7. | Packaging, Transport, Storage | 16. | Protection against radiation |
| 8. | Undesirable side-effects minimised & Risks<Benefits | 17. | **Electronic programmable systems** |
| 9. | Annex XVI “no risk at all” or “no more than the maximum acceptable risk” | 18. | Active devices and devices connected to them |
| | | 19. | Requirements for AIMD |
| | | 20. | Protection against mechanical and thermal risks |
| | | 21. | Protection against the risks posed to the patient or user by supplied energy or substances |
| | | 22. | Protection against the risks posed by medical devices intended for use by lay persons |
| | | 23. | **Information Supplied** |
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
Just some of the challenges.....

- Content and format of NB assessment output?
- Variations that impact safety and performance aspects of the device part after initial MAA is granted?
- NB opinion required as part of initial MAA or can it be done concurrent to MAA review?
- NB verification of the QMS?
- NB assessment of clinical data?
- Interaction between NB, CA, EMA?
- Format of technical documentation?
- Sterility aspects?
- Labelling requirements?
- Lifecycle management?
- Post market data specific to device part?
- What if NB provides a negative opinion?
- Will NB resource be a problem?
- Recertification requirements?
- NB timelines?
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:
  - 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 utilizing 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 utilizing 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:

- transplants, tissues or cells of animal origin, or their derivatives, or products containing or consisting of them; however this Regulation does apply to devices manufactured utilising tissues or cells of animal origin, or their derivatives, which are non-viable or are rendered non-viable
- 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
- Products...... that contain or consist of viable biological substances or organisms, including living micro-organisms, bacteria, fungi or virus in order to achieve or support the intended purpose of the product;
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

- non-viability of the human tissues or cells
- donation, procurement and testing
- risk / benefit
- Seek opinion from Competent Authority (2004/23/EC)
Annex IX, 5.3.1: Tissues or cells of human origin or their derivatives

Notified Body Assessment

1. Non-viability of the human tissues or cells
2. Donation, procurement and testing
3. Risk / benefit
4. Seek opinion from Competent Authority (2004/23/EC)

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

Notified Body Assessment

Due consideration to all comments

Scientific opinion of CA to be included in NB report

Convey final decision to CA

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

Notified Body Assessment:

- Scientific opinion of CA to be included in NB report
- Unfavourable scientific opinion
- Assess changes
- Convey final decision to CA
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:

- Impact on quality and safety (risk/benefit)
- NB to consult with original CA
- Scientific opinion of CA to be included in NB report
- Due consideration to all comments
- Convey final decision to CA

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

Change Consultation:

Impact on quality and safety (risk/benefit)

NB to consult with original CA

Scientific opinion of CA to be included in NB report

Unfavourable scientific opinion

Convey final decision to CA

Due consideration to all comments
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

- Risk analysis / risk management
- Justification
- Inactivation / elimination studies or literature reviews
- Source control
- Approach to auditing
- TSE certificate of suitability
Annex IX, 5.3.2: Tissues or cells of animal origin or their derivatives

Notified Body Assessment
722/2012 Consultation

- NB compiles SER
- SER submitted to coordinating CA
- Coordinating CA circulates SER to other member state CAs
- CAs submit comments on SER

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

- NB to give due consideration to comments
- Justify if comments are not taken into account
- Convey final decision to coordinating CA
- NB to assess changes
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.
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.
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.