BSI's perspective on Article 117 and Drug/ Device Combinations

Dr Jennifer Durrant: Global Head, Medicinal & Biologics Team

Dr Jonathan Sutch: Medicinal Expert

1st July 2020

By Royal Charter

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Agenda

- About BSI
- BSI Regulatory Services
- Introduction to the Medicinal & Biologics Team
- Article 117
  - Impact
  - Review Process and Timelines
  - Documentation requirements
  - Lessons Learned
  - NBOp output
  - Design Changes

About BSI

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BSI – is a purpose-driven organization underpinned by Royal Charter

Why we exist	What we believe in	What we do	How we do it
Our Purpose	**Our Values**	**Our Mission**	**Our behaviours**
Inspiring trust for a more resilient world	Integrity Respect Expertise	To share knowledge, innovation and best practice to help people and organizations realize their potential and make excellence a habit	Client-centric Agile Collaborative

Our approach

Our business is enabling others to realize their potential and perform better. We provide a unique combination of complementary services and solutions managed through four global business streams:

Consulting Services

- Consultancy
- Supply Chain Solutions

Knowledge

- Standards Development
- Services
- Information Solutions

Assurance Services

- Systems Certification
- Product Certification
- Training

Regulatory Services

- Systems and Product Certification of Medical Devices

We operate across many sectors, and focus on four areas of specialization:

- Aerospace and Automotive
- Health
- Food and Retail
- Built Environment

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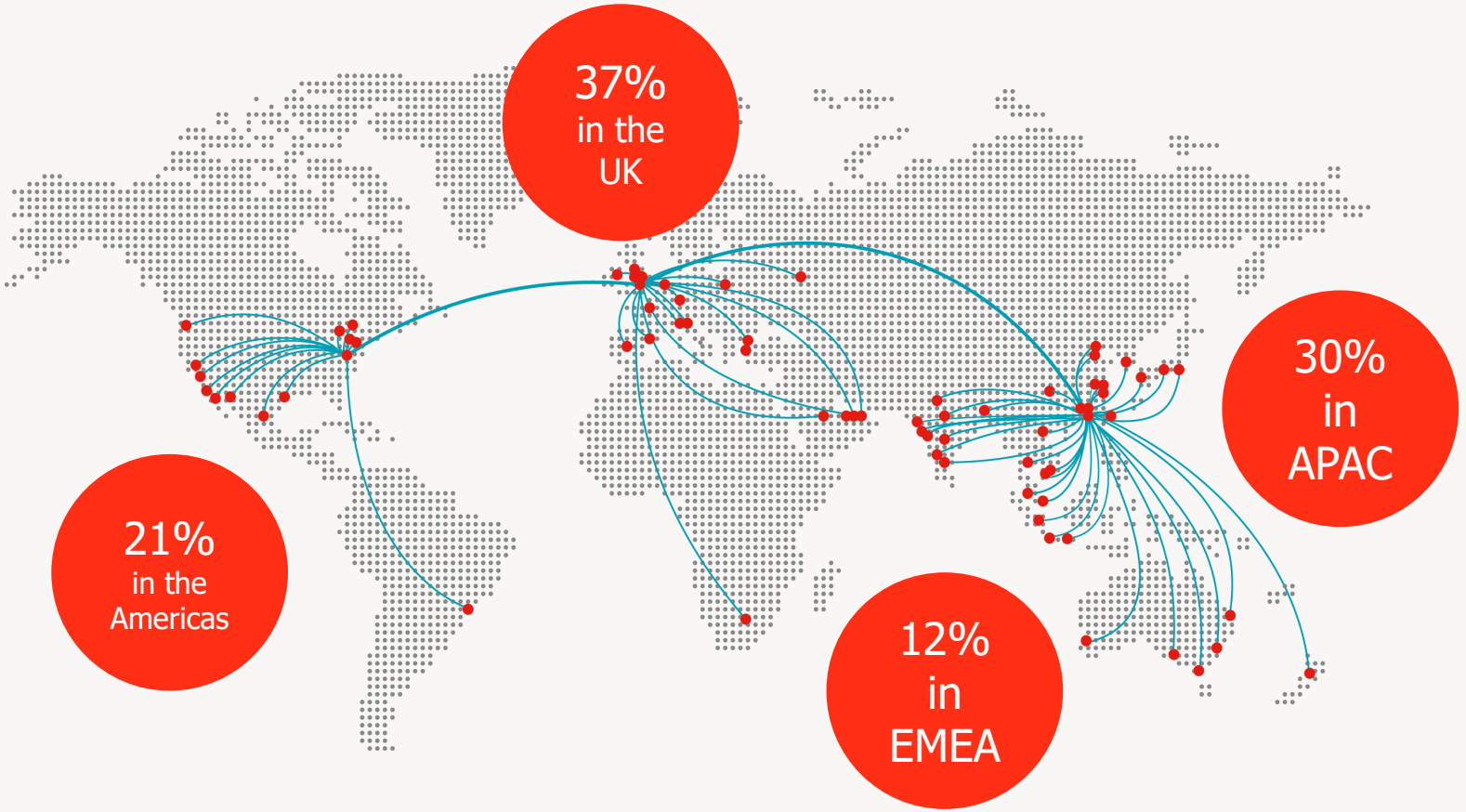
Our global network of people

BSI is an integrated global enterprise, able to serve clients from 84 offices in 31 countries across the world.



Our **5,089** worldwide colleagues are operating in **195** countries with

- **893** supporting Business Delivery through HR, IT, Finance, Management, Legal, Communications and Facilities.
- **724** in Sales and Business Development
- **547** in Consulting
- **1,422** in System Certification
- **177** in Product Certification
- **700** in Regulatory Services
- **210** in Marketing

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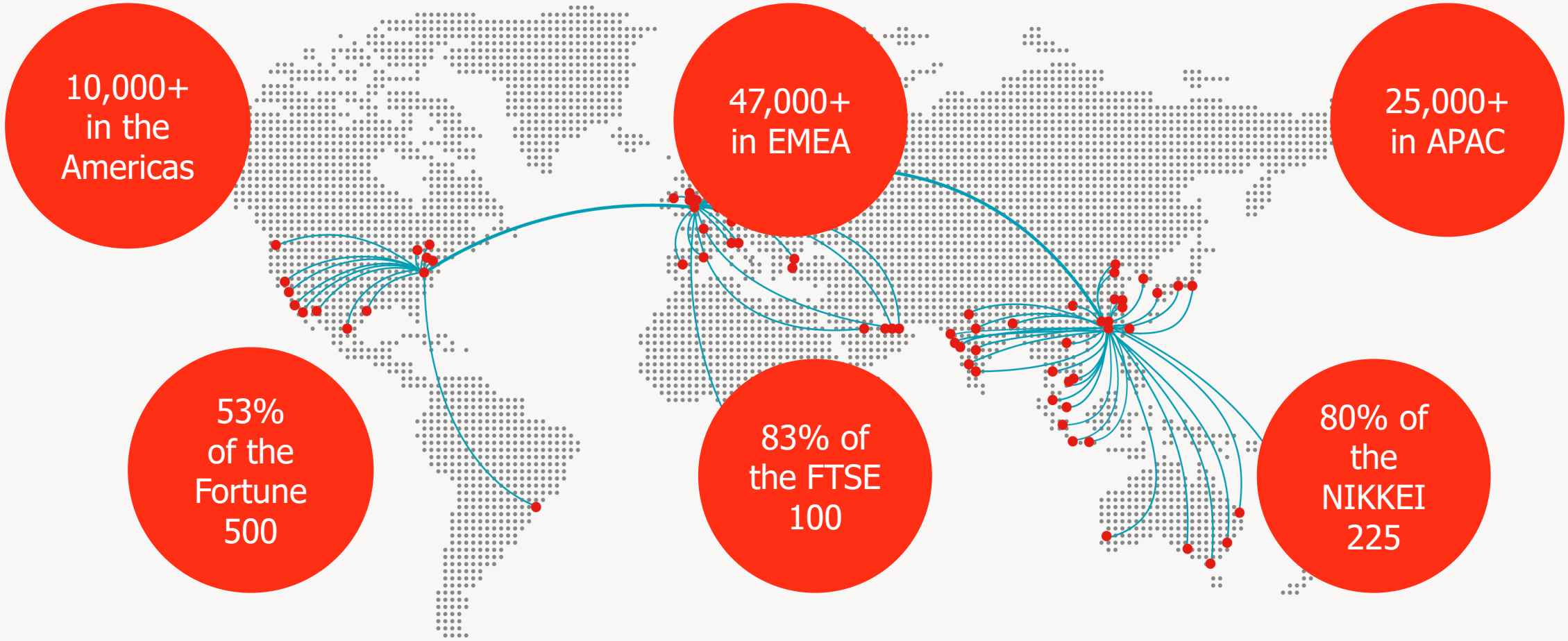
Serving a global network of clients

Our 84,000 clients range from globally recognized brands to small local companies in 195 countries across a range of industries.



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BSI Regulatory Services

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About BSI Regulatory Services

96%	**96% of the world's top 25** medical device manufacturers work with BSI
700+	**Over 700** colleagues worldwide
Market leader	**Largest Notified Body** globally; BSI is a market leader
Two full scope Notified Bodies	**Designated with full scope** to the MDD, AIMDD, IVDD, MDR and IVDR
Designated and Accredited	**Designated by** MHRA, IGJ **Accredited by** UKAS, SCC and RvA **Recognized by** MHLW/PMDA, TFDA, MDB, INMETRO, MDSAP RAs

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

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Medicinal & Biologics Team

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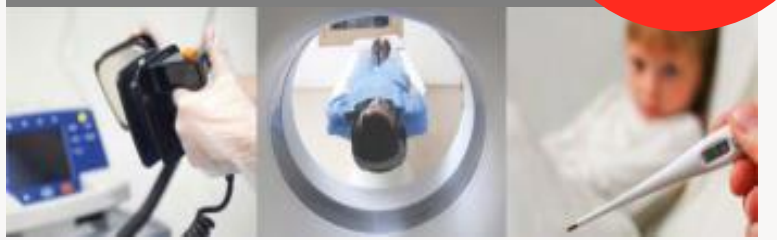
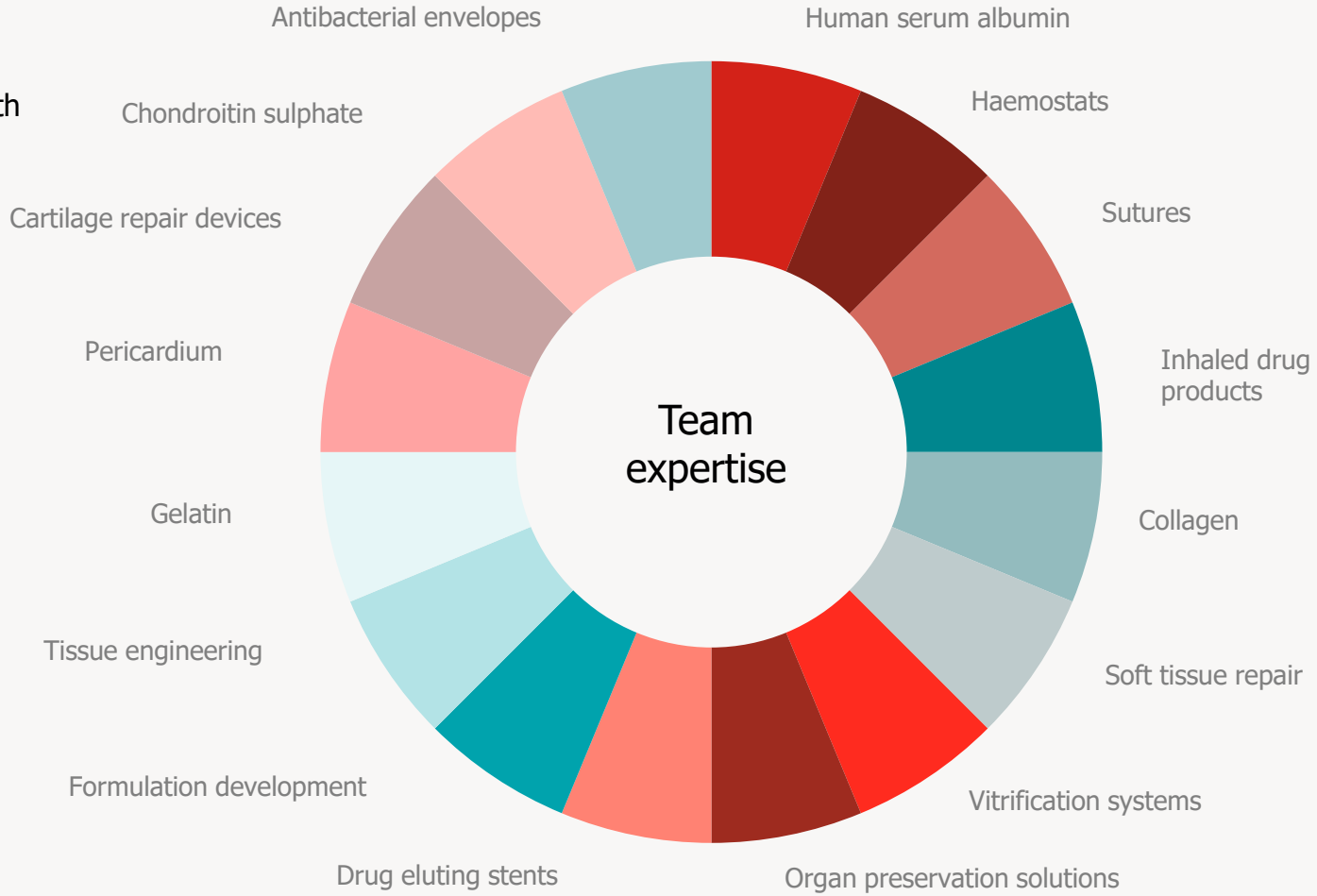
Unrivalled expertise from BSI's Medicinal and Biologics team

- 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 20 graduate degrees between them.

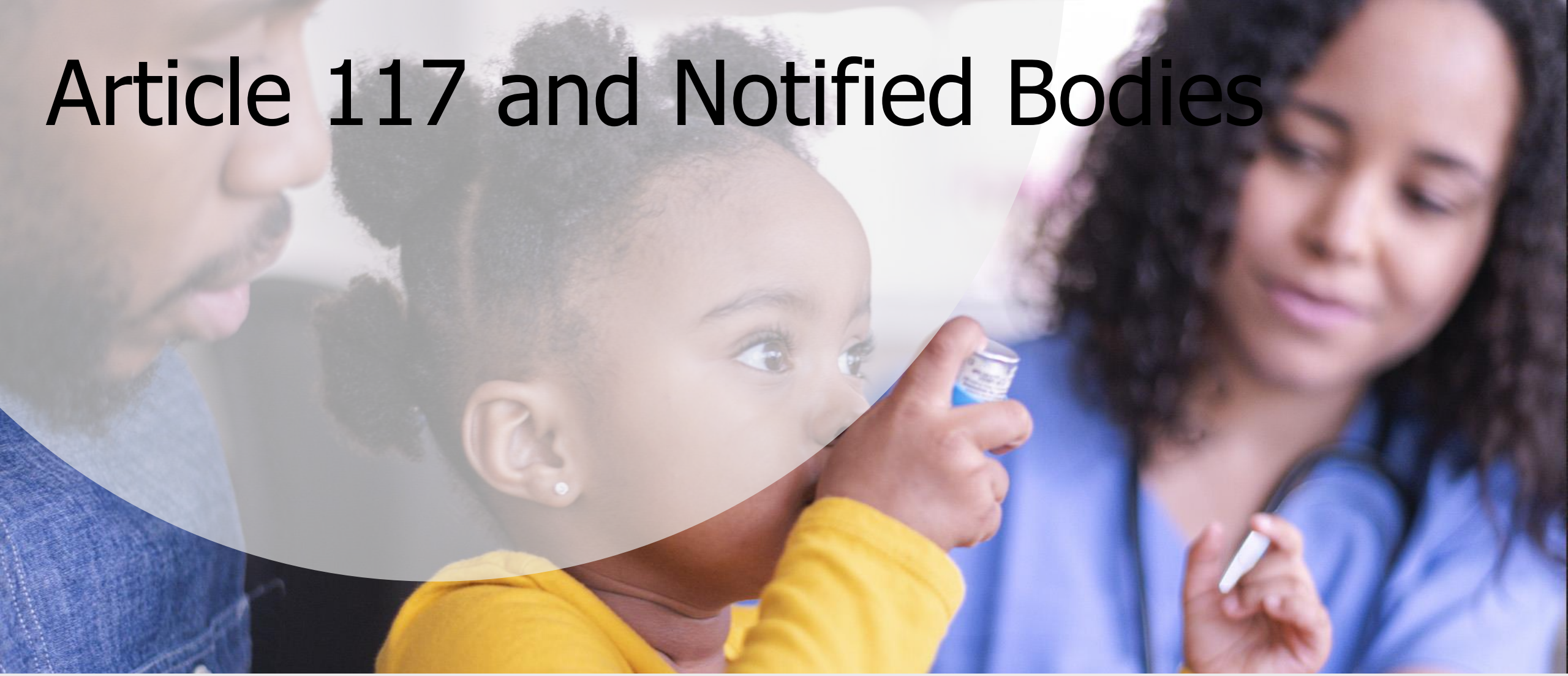
The BSI Medical Devices Medicinal and Biologics team combined experience

196
YEARS





Article 117 and Notified Bodies



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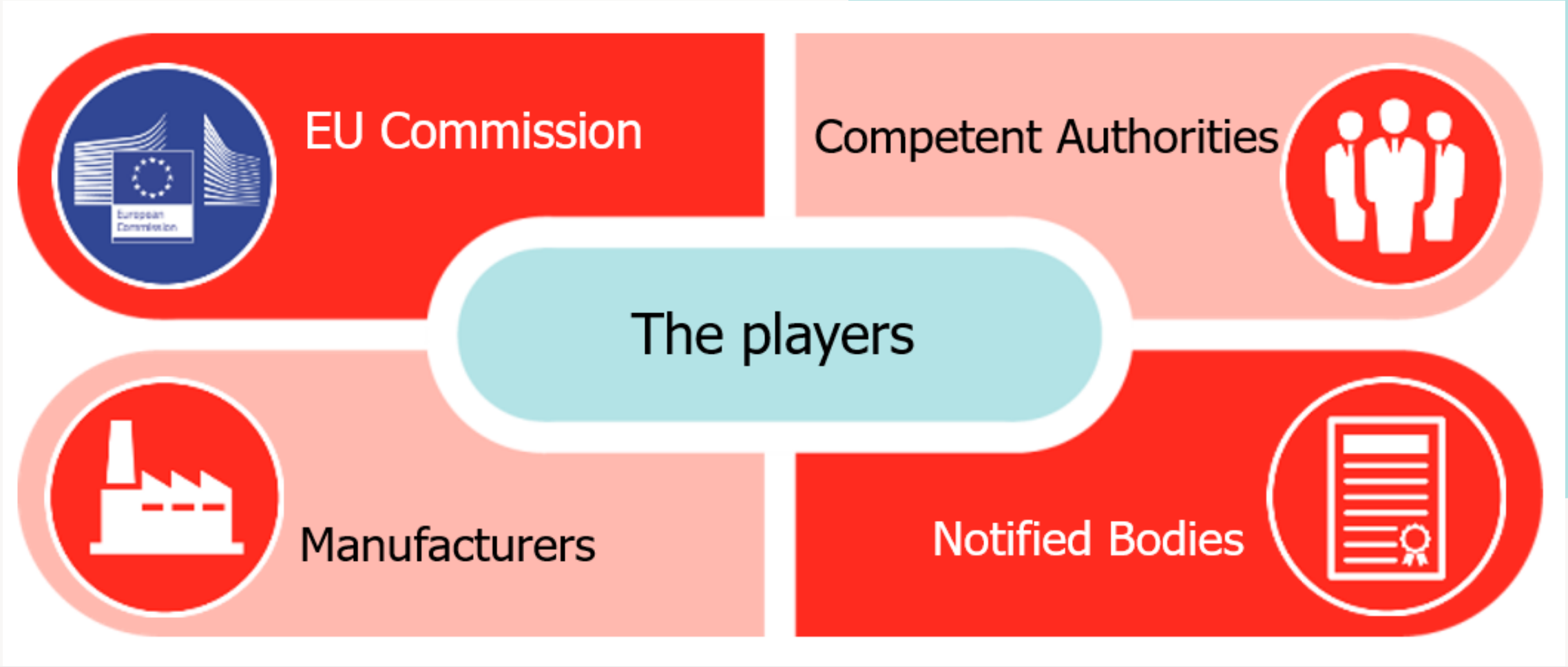
Who is involved in the Article 117 Process



Article 117

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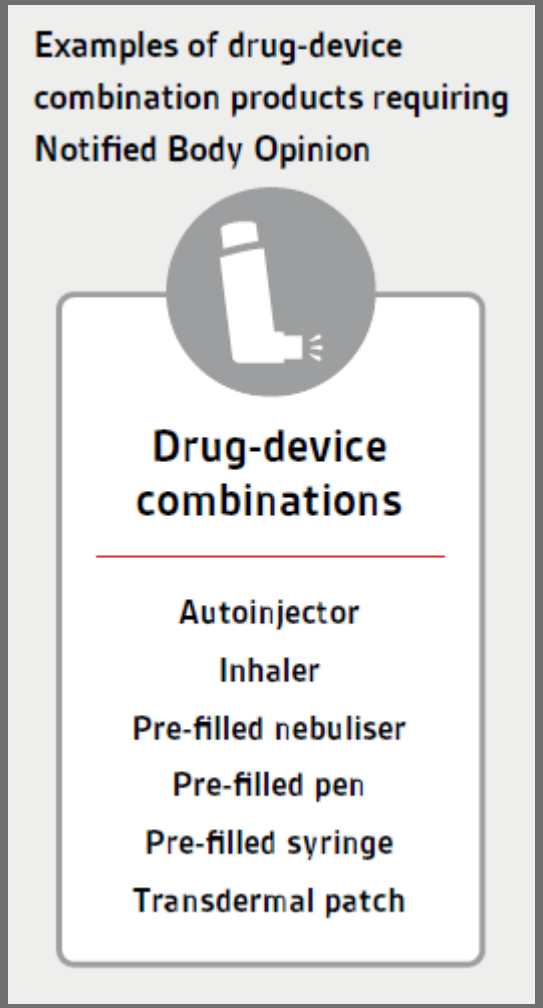
Article 117 with BSI

- What is Article 117?
  - What is in scope and what is out of scope
- The process for DDC manufacturers
- BSI process
- Documentation requirements
- Output of the process
- Guidance
- https://www.bsigroup.com/globalassets/meddev/localfiles/en-gb/brochures/mdr-article-117-drug-device-combination-products-application-process-brochure.pdf



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.

Drug Device Combinations-

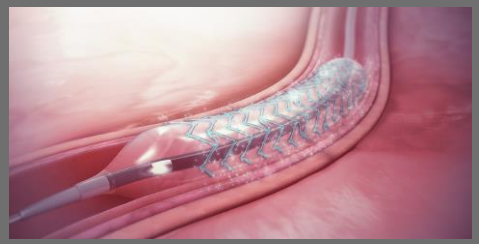
Single integral, exclusively for use, not reusable

9. Any device which is intended to administer a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC shall be governed by this Regulation, without prejudice to the provisions of that Directive and of Regulation (EC) No 726/2004 with regard to the medicinal product.

However, if the device intended to administer a medicinal product and the medicinal product are placed on the market in such a way that they form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable. 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 of the single integral product are concerned.

- Example DDCs in scope

- Not in scope



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Current Process for Drug Device Combinations

Medical Device intended to administer a Medicinal Product

Autoinjector

Pre-Filled Pen

Pre-Filled Syringe

Inhaler

Pre-Filled IV Bag

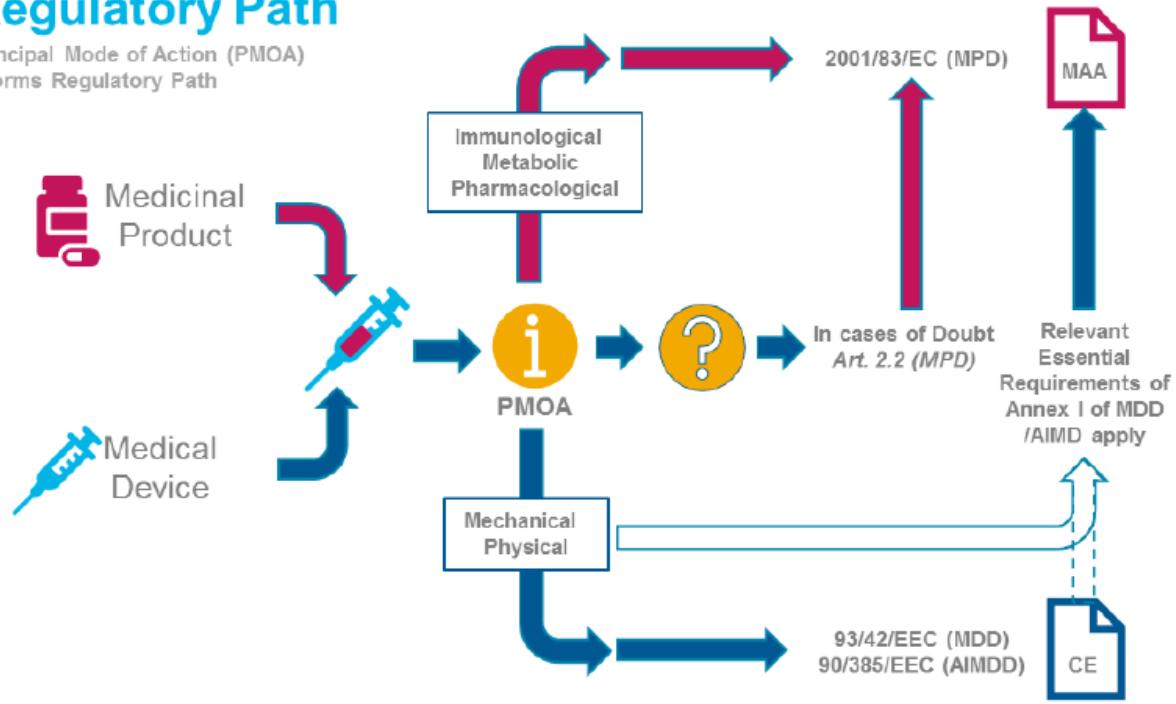
Transdermal Patch

single integral product, not reusable

AS-IS PROCESS

Regulatory Path

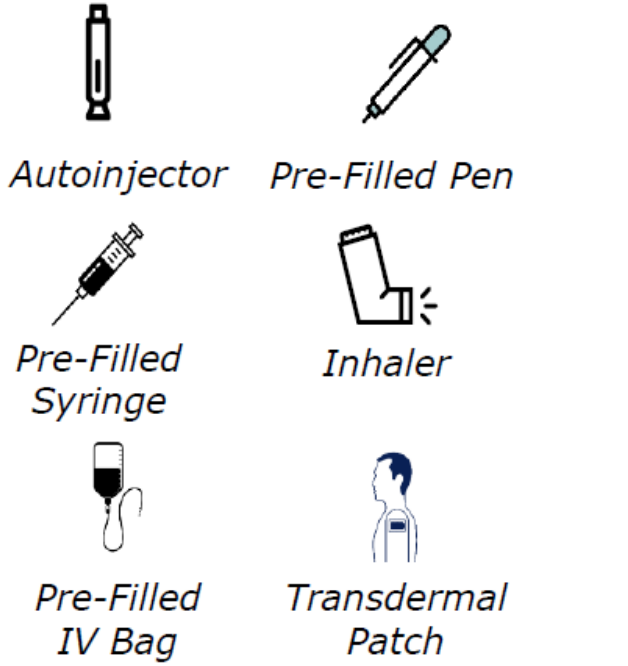
Principal Mode of Action (PMOA) Informs Regulatory Path



Credit: Paul Scannell, from TOPRA 2019

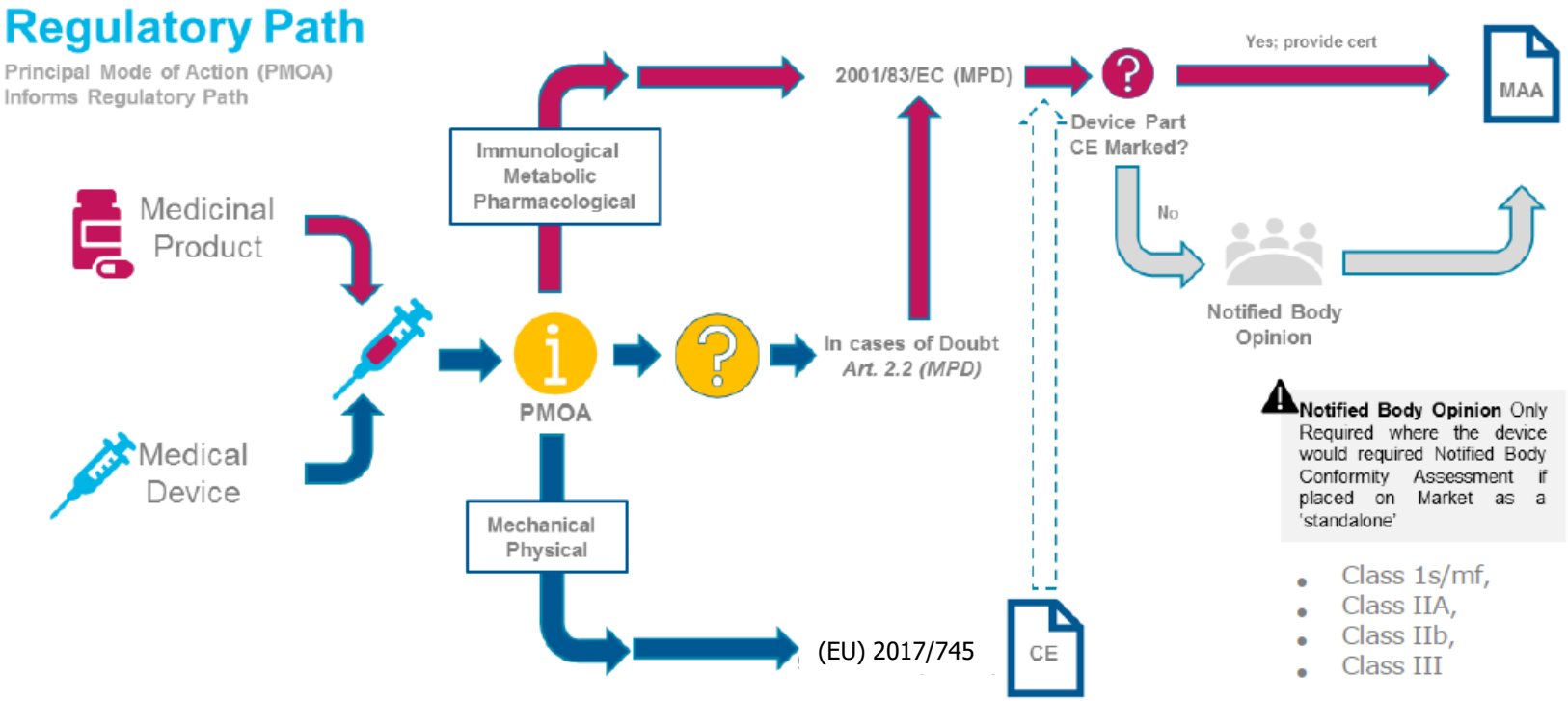
Future Process for Drug Device Combinations- Under MDR

Medical Device intended to administer a Medicinal Product



single integral product, not reusable

TO-BE PROCESS (from 26 May 2021)



Credit: Paul Scannell, from TOPRA 2019

Impact of Article 117 on Pharmaceutical Industries

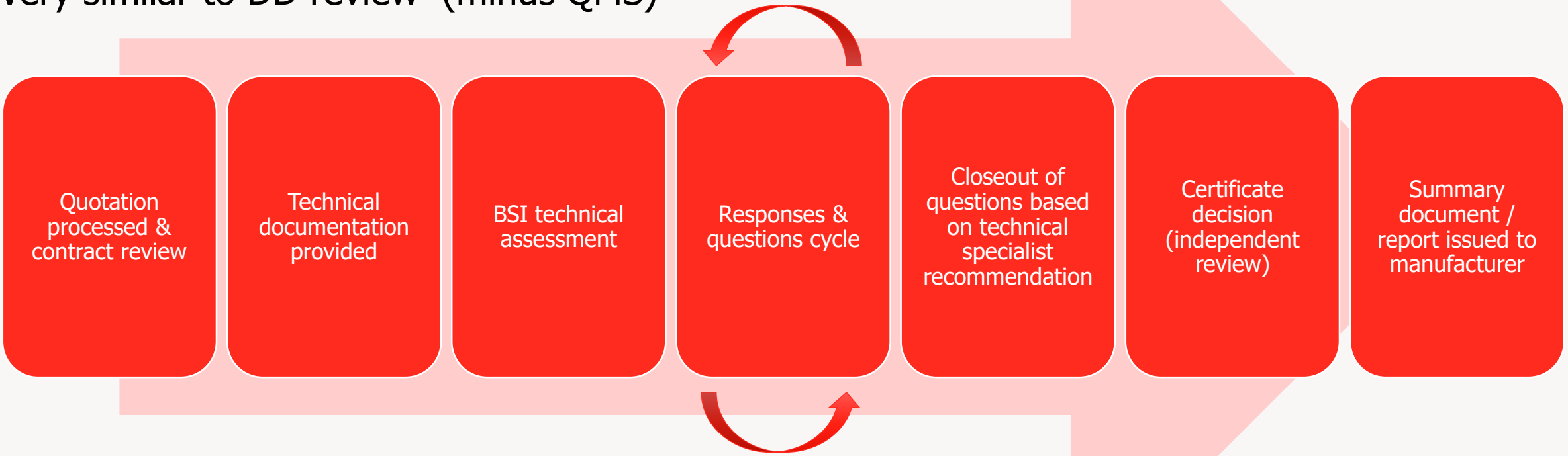
- The **relevant** General Safety and Performance Requirement (GSPR) of MDR Annex I will apply to the device component.
- Need to find & work with a designated Notified Body
  - This is a big concern- availabilities and timelines BSI is open to this new business
- Obtain Notified Body assessment report
- Include this assessment report in the MAA
- No grandfathering so any **new** submission after **26th May 2021** needs NBOp

- **In case of changes to device,** Notified Body reassessment required for significant change to the device

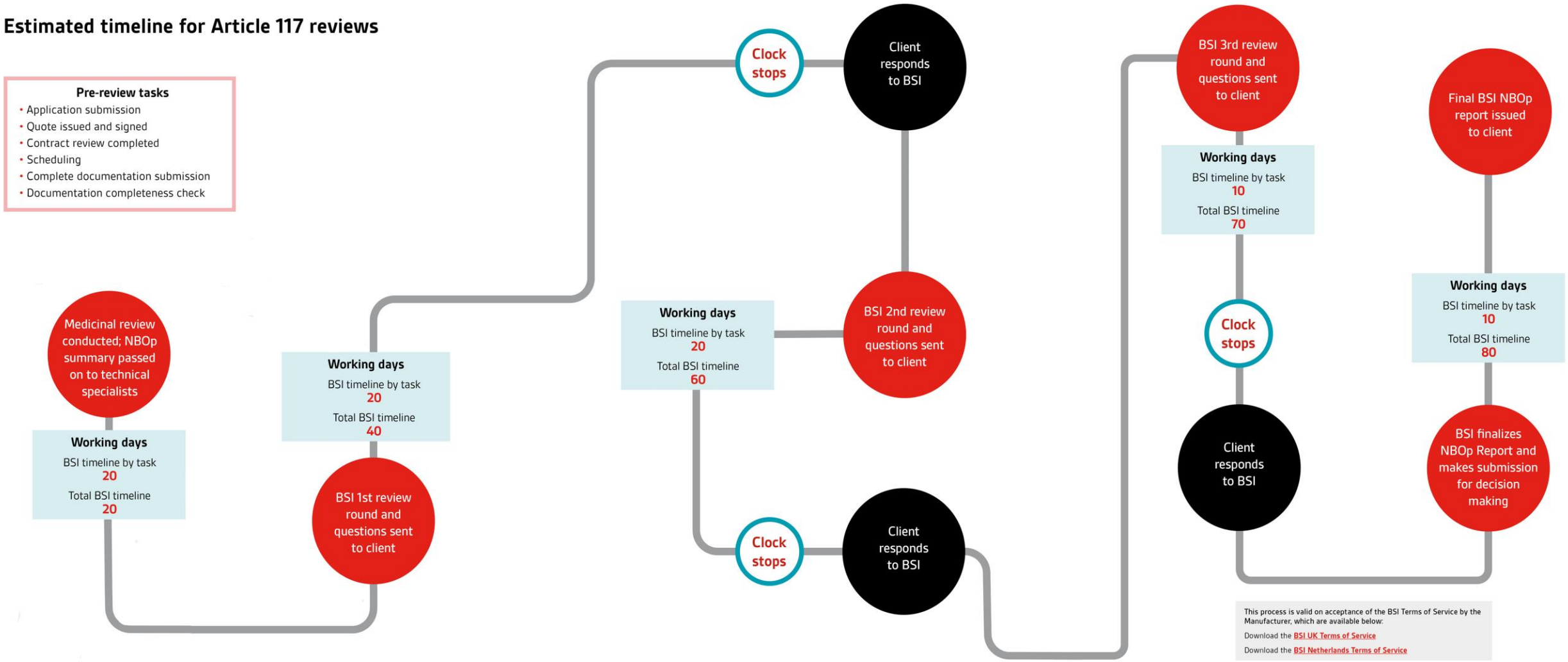
Notified Body Assessment: Article 117

BSI Review Process:

Very similar to DD review (minus QMS)



Estimated timeline for Article 117 reviews



Annex I – Safety and performance requirements

1. Safe, Perform as Intended, State of the Art  

2. Risk reduction as far as possible
3. **Risk Management** 
4. Risk Control
5. Risk of **Use Error** 

6. Lifetime 
7. Packaging, Transport, Storage 
8. Undesirable side-effects minimised & Risks<Benefits
9. Annex XVI "no risk at all" or "no more than the maximum acceptable risk" 

10. **Chemical, Physical & Biological** Properties 
11. Infection & Microbial Contamination 

12. Devices incorporating a medicinal product and devices composed of substances that are absorbed by or locally dispersed in the human body
13. Devices incorporating **materials of biological origin** 
14. Construction and **interaction with the environment**
15. Devices with a diagnostic or measuring function 
16. Protection against radiation 
17. **Electronic programmable systems** 
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**  

bsi. If you believe a GSPR is not relevant always state why, rather than just N/A

Article 117 Documentation

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.

https://www.team-nb.org/wp-content/uploads/2020/04/Team-NB_Position-Paper_on-Documentation-Requirements-Article117-V1.pdf

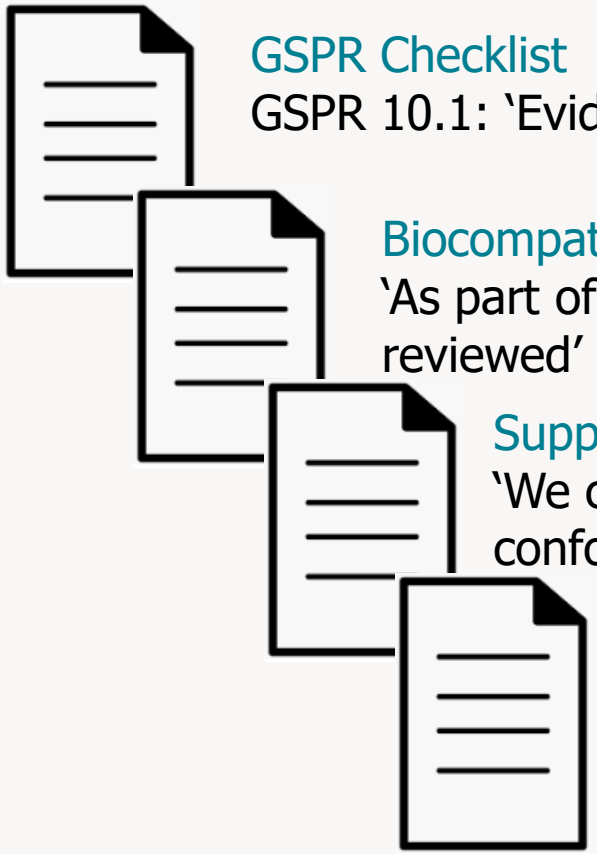
Documentation Learning Points

GSPR Checklist to show what the evidence is and where it is in the document (hyperlinked)

Detail from subcontractors and suppliers

If it is all there and accessible the review is smoother

Documentation Learning Points- Example



GSPR Checklist

GSPR 10.1: 'Evidence is presented in Biocompatibility Summary Report'

Biocompatibility Summary Report

'As part of an ISO 10993-1 approach supplier statements of conformity were reviewed'

Supplier statements of conformity

'We confirm studies compliant with ISO 10993-1 have demonstrated conformity…'

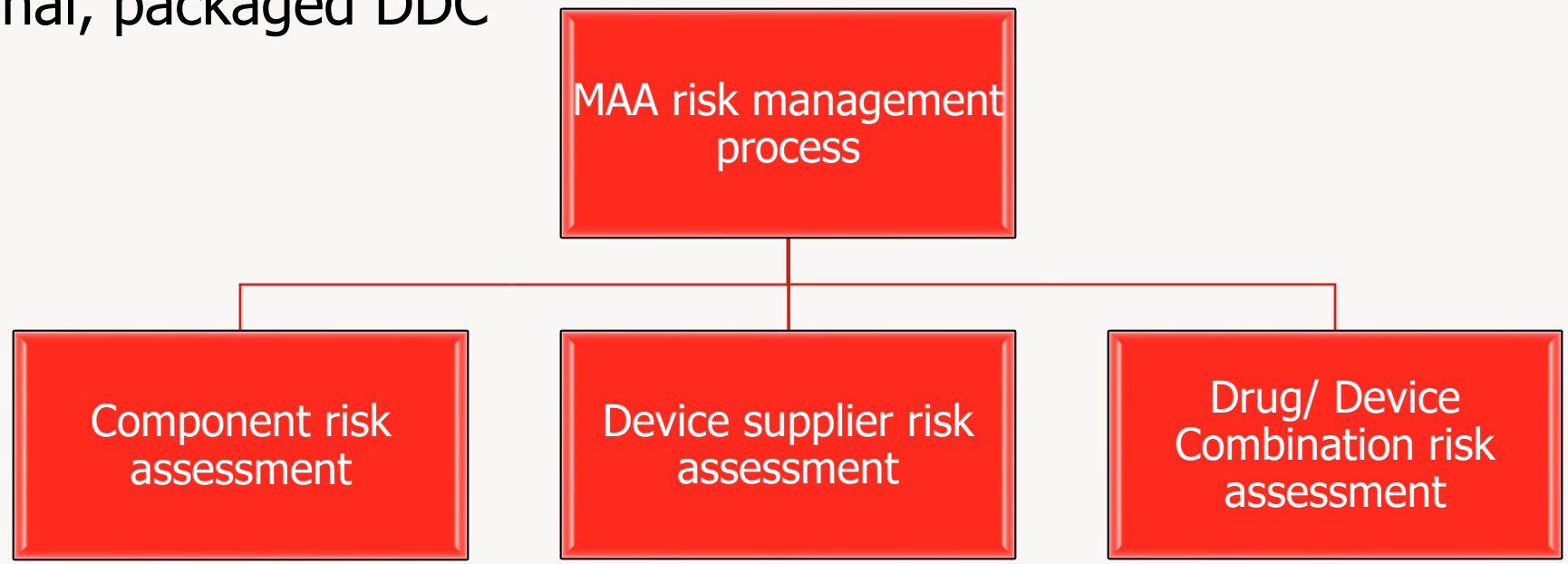
ISO 10993-1 Assessment of Biocompatibility of component X

Data, Data, Data, Data, Discussion, Conclusion

In order to verify compliance to the GSPR the notified body will want to see all of these reports.

Documentation Learning Points

- Conformity to GSPRs may be demonstrated with data:
  - On component
  - On device
  - On final, packaged DDC

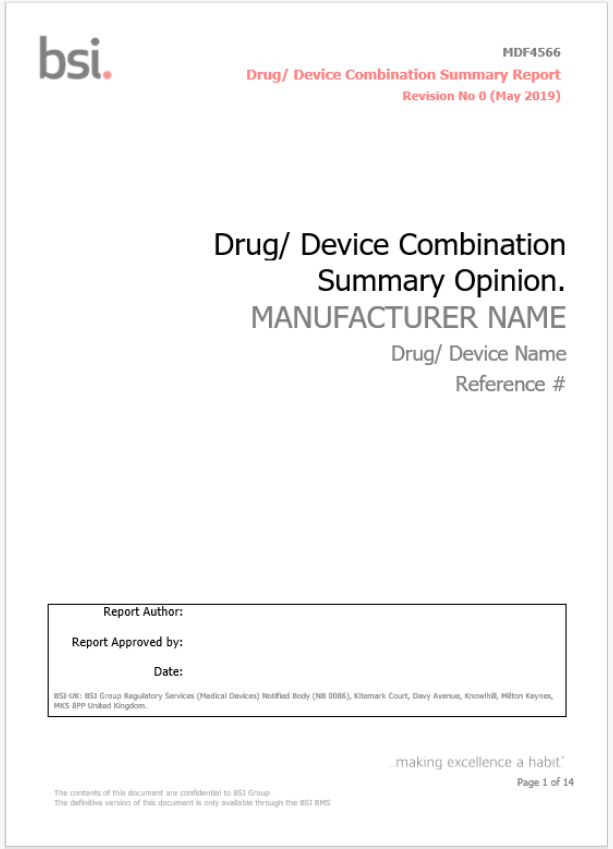


Notified Body Opinion

Will take the form of a report

- Clear which version of the device has been evaluated
- Clear to Competent Authority what has been looked at
  - Sufficient detail to avoid duplication/ overlap
  - Sufficient detail to give confidence
- Any gaps clear to Competent Authority

- NBOp template offered as addition to QWP/BWP guideline
  - Team-NB will looking at publishing separately.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MDF4566

Drug/ Device Combination Summary Report

Revision No 0 (May 2019)

Drug/ Device Combination Summary Opinion.

MANUFACTURER NAME

Drug/ Device Name

Reference #

Report Author:

Report Approved by:

Date:

BSI-UK: BSI Group Regulatory Services (Medical Devices) Notified Body (NB 0086), Kitemark Court, Davy Avenue, Knowlhill, Milton Keynes, MK5 8PP United Kingdom.

...making excellence a habit.

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The contents of this document are confidential to BSI Group
The definitive version of this document is only available through the BSI BMS

Notified Body Opinion

18.8	Design & manufacture – avoid unauthorized access	☒**YES** ☐**NO** ☐**PARTIAL**	The product is provided in "tamper proof" packaging. IFU warns not to use the device if the seal is broken and to perform a visual inspection and not use the device if it looks damaged or if it has been dropped.
19.1	Active implantable devices – reduce risks as far as possible connected with use of energy sources, medical treatment, where maintenance and calibration are impossible	☐**YES** ☐**NO** ☐**PARTIAL** ☒**N/A**	N/A – appropriate rationale given

Article 117 – Guidance

- Current Guidance
- Areas where further guidance is needed
  - Classification
  - Platforms
  - Changes

Guidance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 April 2020
EMA/CHMP/QWP/BWP/259165/2019
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the quality requirements for drug-device combinations

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

21 October 2019 Rev.1
EMA/37991/2019
Human Medicines Evaluation Division

Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)

TEAM NB
The European Association Medical Devices - Notified Bodies

Editor :	Team-NB	Adoption date :	01/04/2020	Version 1

Team-NB Position Paper

on Documentation Requirements for Drug Device Combination Products

Falling in the Scope of Article 117 of MDR 2017/745.

A note on Classification of DDCs

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

Type of integral device included in the MAA	New submissions as of 26th May 2020
Class I (sterile, measuring or reusable surgical instrument*), Class IIa, Class IIb Class III	The marketing authorisation dossier should include a **Declaration of Conformity or EU notified body certificate** for the medical device, where available. If the above mentioned documentation is not available then **an opinion** from a notified body** must be provided for the medical device
Class I (non-sterile, non-measuring, or non-reusable surgical instrument)	The marketing authorisation dossier should include a **Declaration of Conformity** for the medical device, where available.
* the reader should note that integral DDC as referred to in second subparagraph of Regulation 2017/745 Article 1(9) are not reusable **opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to Regulation 2017/745	

Changes

In cases where the MAH introduces substantial changes to the medical device component, a new (updated) EU certificate / declaration of conformity / opinion from a notified body will need to be provided as part of the variation/extension application, as appropriate.

Changes to the device component are considered substantial if the changes affect the performance and safety characteristics of the device.

It is the responsibility of the marketing authorisation holder to determine if the changes are substantial and EMA/NCAs expect that the MAHs liaise with the notified body and submit to EMA/NCA the necessary documentation as part of a variation/extension application.

This requirement applies to all marketing authorisations, even those that had complied with Article 117 MDR with their initial MAA.

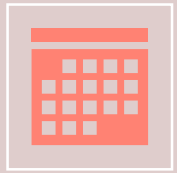
- Applies to all marketing authorisations
- Substantial changes need NBOp as part of variation
  - Changes that affect performance and safety characteristics
- Responsibility of MAH to determine if changes are substantial
  - Do liaise with NB to obtain NBOp
  - Don’t liaise with NB to determine if change is substantial

Platforms

- Not mentioned in QWP/BWP Guideline
- Still being discussed by industry groups including Team-NB
- Needs agreed definitions and framework
- Savings possible for subsequent DDCs with same ‘platform’ with BSI

Key Take-aways

Do not delay your Article 117 plans



Engage and plan with your NB

Drug-device combination products under MDR Article 117

Are you a manufacturer of drug-device combination products? If so, you need to be aware of the changes in Article 117 of the Medical Device Regulation (MDR).

Introduced by the European Commission under the Medical Devices Regulation (MDR), Article 117 requires manufacturers placing drug-device combination products onto the market as an integral device and marketing them as a "medicinal product" to seek a Notified Body Opinion (NBOp).

The notified body then confirms whether the device is compliant with the relevant General Safety and Performance Requirements (GSPR) and provides an NBOp Report to the manufacturer to include in the Market Authorisation Application (MAA).

Examples of drug-device combination products requiring NBOp include autoinjectors, inhalers, pre-filled nebulisers, pre-filled pens, pre-filled syringes and transdermal patches.

Manufacturers of combination products will need to obtain the services of a Notified Body; come and talk to BSI early in your planning.

Questions and Answers

https://www.bsigroup.com/en-GB/medical-devices/technologies/drug-device-combination-products/

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