Notified body experience with NBOps

Oct 2021

Jonathan Sutch, PhD
Senior Medicinal Specialist

By Royal Charter

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Overview

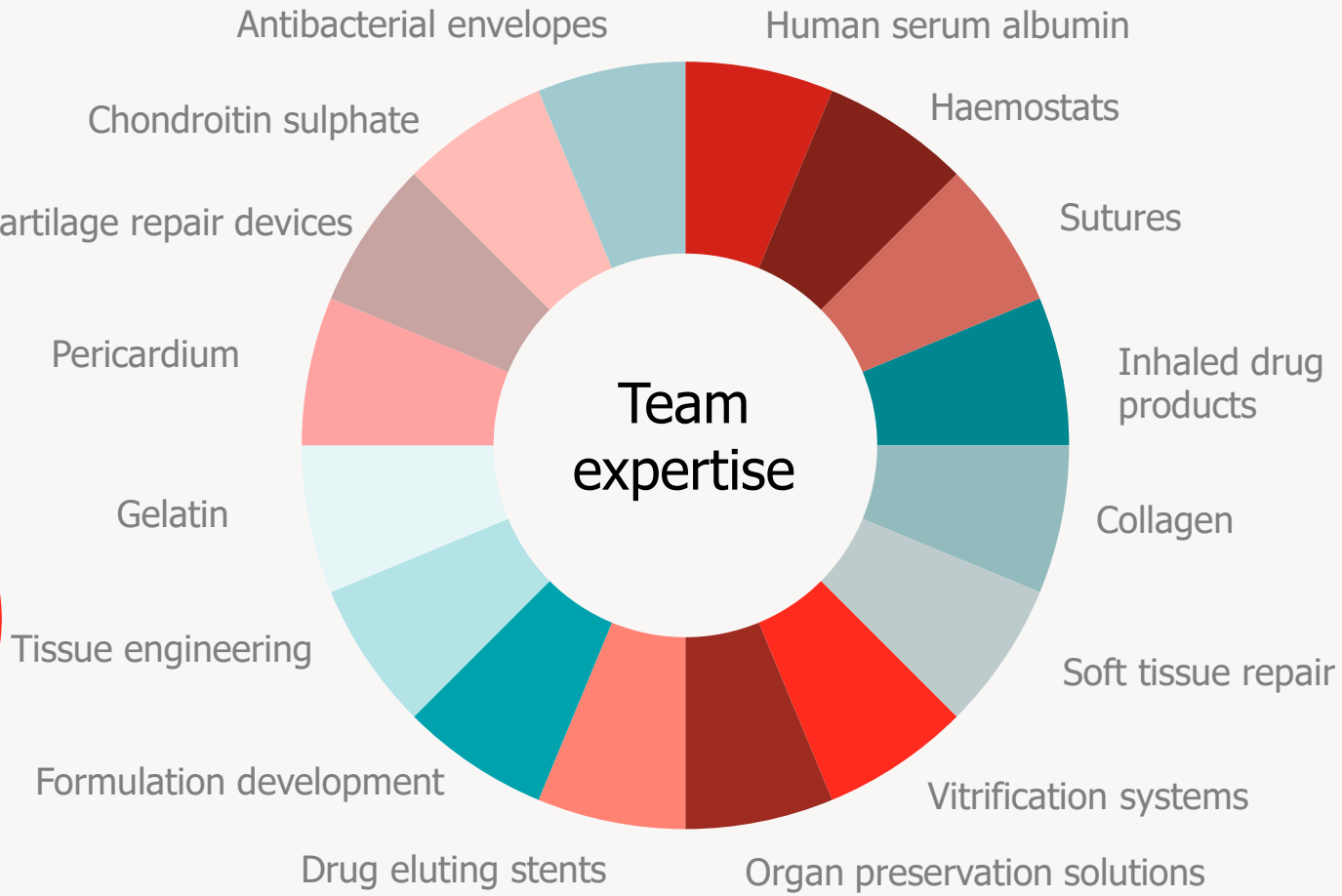
- Experience and learnings from NBOp reviews so far
- Dealing with platform technologies and opportunities for the future
- Collaboration efforts on consistency across NBs and competent authorities

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.

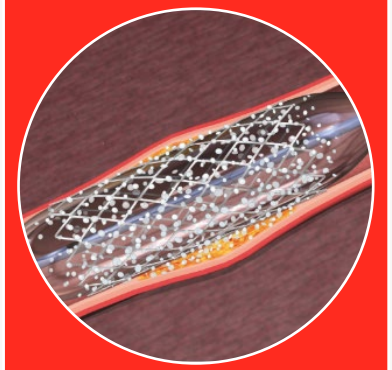
The BSI Medical Devic
Medicinal and Biologics
combined experience

107
YEARS



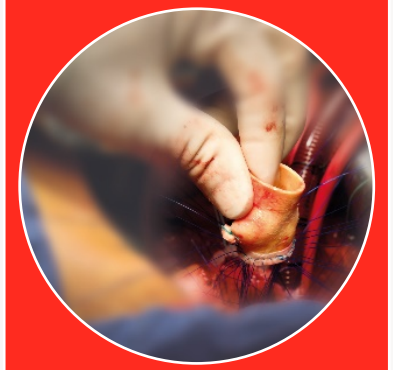
Correct as of July 2018

Medicinal & Biologics Team Scope



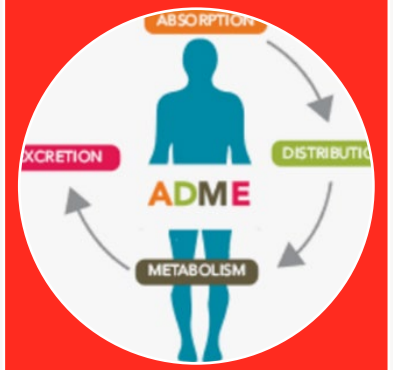
Device-drug Combinations

Drug-device combinations



Devices utilising materials of biological origin

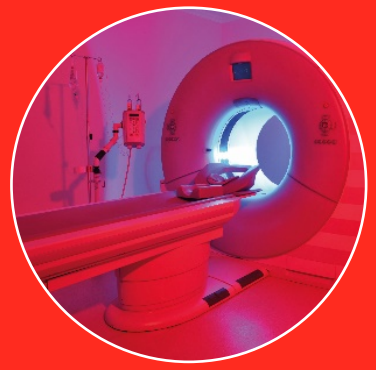
IVF/ART, Organ Preservation



Devices Composed of Substances

Active devices intended to administer medicines

Medicinal & Biologics Team Delivery

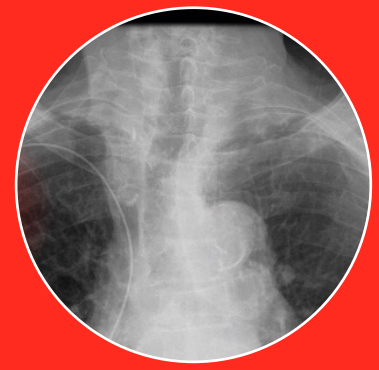


Active Devices Team

General Devices Team

Orthopaedic & Dental Team

Vascular Team



Active Implantable Team

Medicinal & Biologics Team

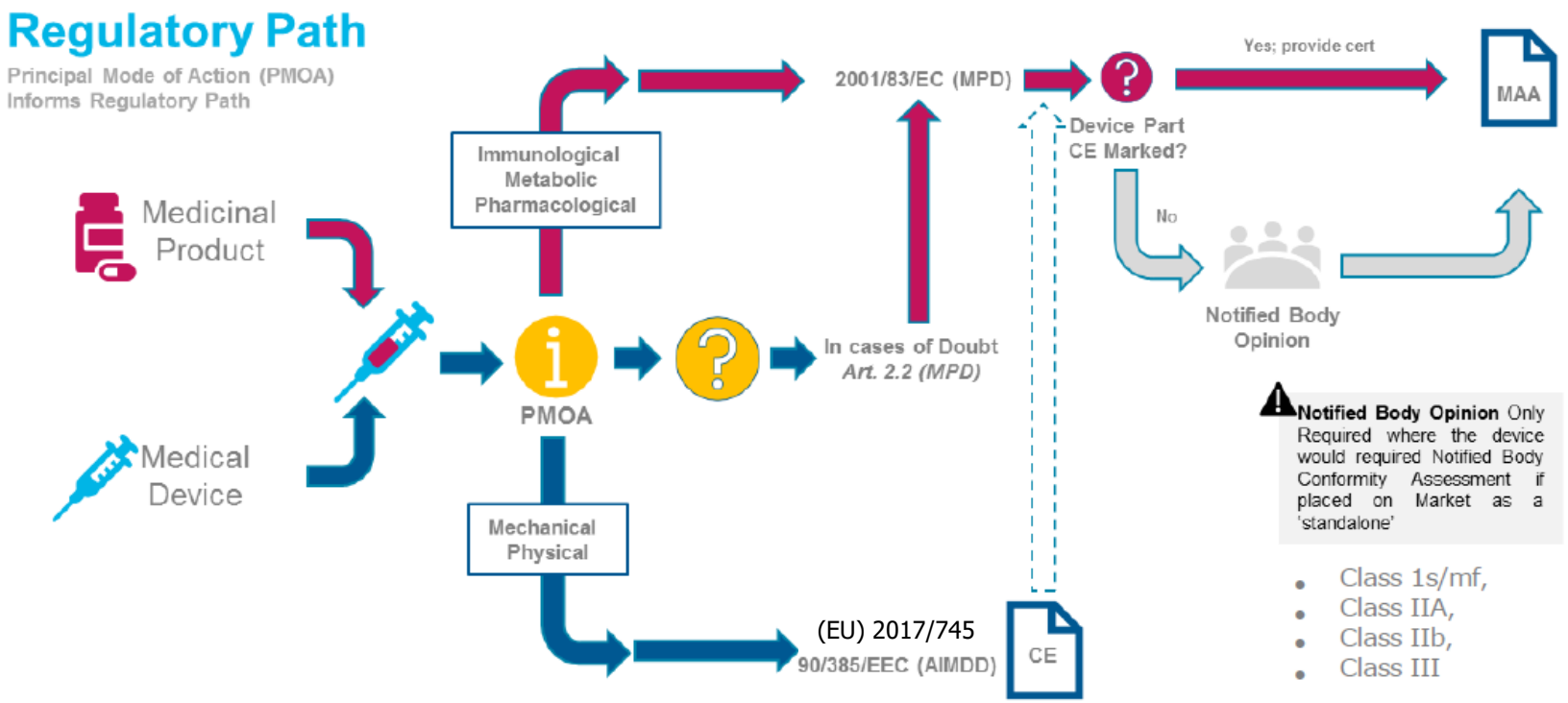
Integral Combinations- Under MDR

Medical Device intended to administer a Medicinal Product

Autoinjector *Pre-Filled Pen*

Pre-Filled Syringe *Inhaler*

single integral product, not reusable

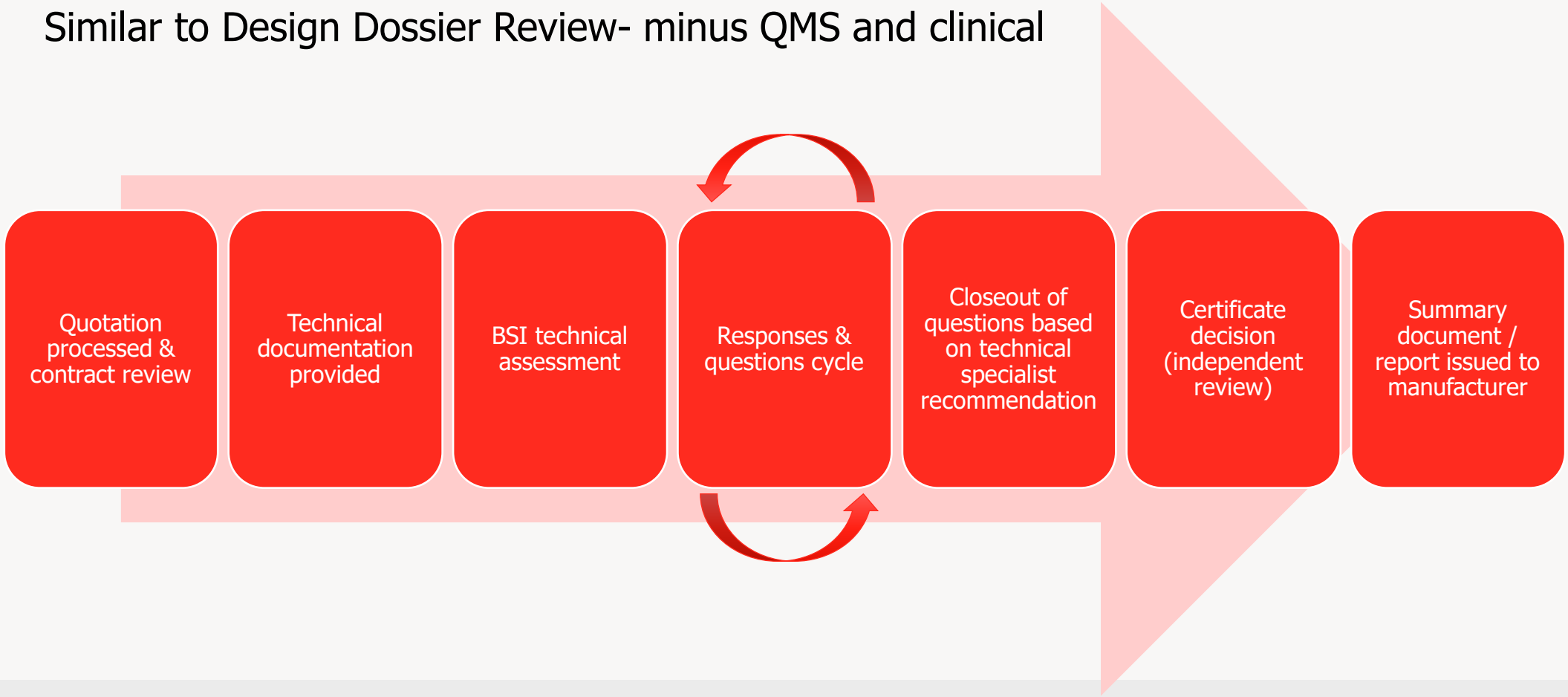


Credit: Paul Scannell, from TOPRA 2019

Notified Body Assessment: Article 117

BSI Review Process:

Similar to Design Dossier Review- minus QMS and clinical



Common Questions

01

Clinical Use

Provide key risks, warnings and precautions related to the medicinal substance and the final device together with dose selection and adjustment criteria

02

Overall Process

Please confirm 1. manufacturer's incoming checks and acceptance criteria
2. in-process checks and acceptance criteria 3. final inspection and test, release specifications and acceptance criteria 4. process validations.

03

Administrative

Confirm MAH address vs. contracting entity
Confirm names and addresses of significant subcontractors or crucial suppliers

04

Documentation

Provide the referenced reports related to design and manufacture, biocompatibility
Provide a copy User Requirement Specification for….
.

05

Risk Management

Please provide a copy of the Risk Management Plan and Report for activities carried out at XXX

06

TSE / CRM

Provide copies of the certificates, from those suppliers of components which contain materials of animal origin…

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Guidance


BSI Transitions
Medical Devices Regulation

MDR Documentation Submissions

Best Practices Guidelines

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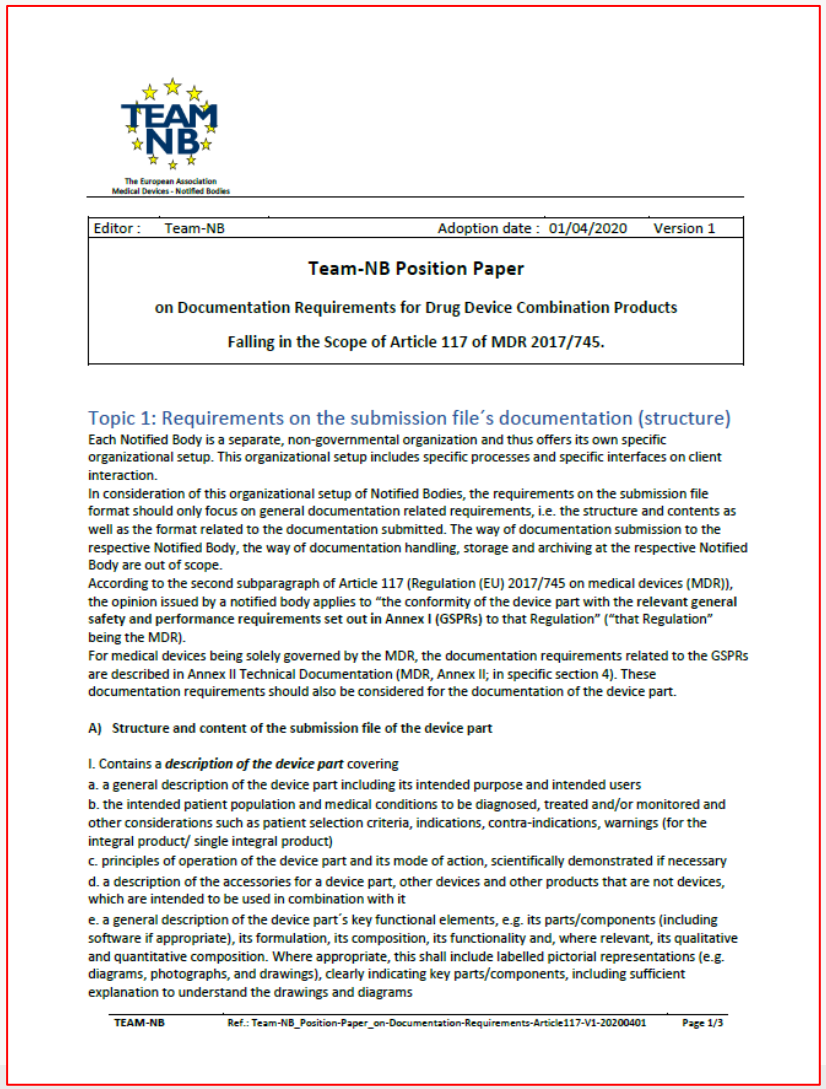
...making excellence a habit.


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.

Topic 1: Requirements on the submission file´s documentation (structure)

Each Notified Body is a separate, non-governmental organization and thus offers its own specific organizational setup. This organizational setup includes specific processes and specific interfaces on client interaction.

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According to the second subparagraph of Article 117 (Regulation (EU) 2017/745 on medical devices (MDR)), the opinion issued by a notified body applies to "the conformity of the device part with the **relevant general safety and performance requirements set out in Annex I (GSPRs)** to that Regulation" ("that Regulation" being the MDR).

For medical devices being solely governed by the MDR, the documentation requirements related to the GSPRs are described in Annex II Technical Documentation (MDR, Annex II; in specific section 4). These documentation requirements should also be considered for the documentation of the device part.

A) Structure and content of the submission file of the device part

I. Contains a ***description of the device part*** covering

a. a general description of the device part including its intended purpose and intended users

b. the intended patient population and medical conditions to be diagnosed, treated and/or monitored and other considerations such as patient selection criteria, indications, contra-indications, warnings (for the integral product/ single integral product)

c. principles of operation of the device part and its mode of action, scientifically demonstrated if necessary

d. a description of the accessories for a device part, other devices and other products that are not devices, which are intended to be used in combination with it

e. a general description of the device part´s key functional elements, e.g. its parts/components (including software if appropriate), its formulation, its composition, its functionality and, where relevant, its qualitative and quantitative composition. Where appropriate, this shall include labelled pictorial representations (e.g. diagrams, photographs, and drawings), clearly indicating key parts/components, including sufficient explanation to understand the drawings and diagrams

Documentation Learning Points

01

GSPR Checklist

Ideally in the format of a checklist

02

TOP Level Summary Reports

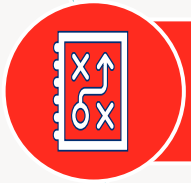
Detail from subcontractors and suppliers

Demonstrates MAH is in control of product

03

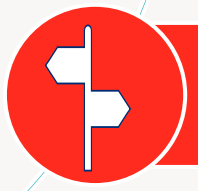
Detailed Reports and Data

Identification of Applicability and Justification



Methods used to demonstrate conformity

Harmonised standards / Common Specifications / Other guidance or applied state of the art solutions



Identification / Traceability of evidence

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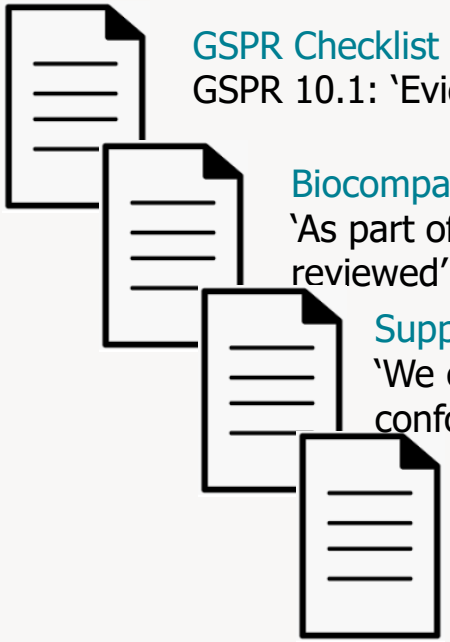
Documentation Learning Points- Example



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'

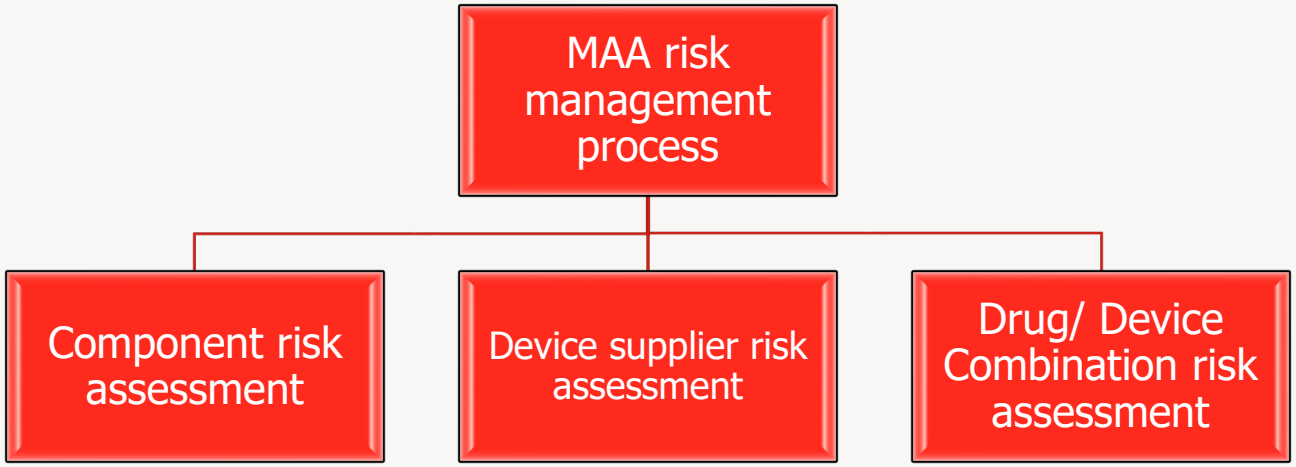
Supplier statements of conformity

'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

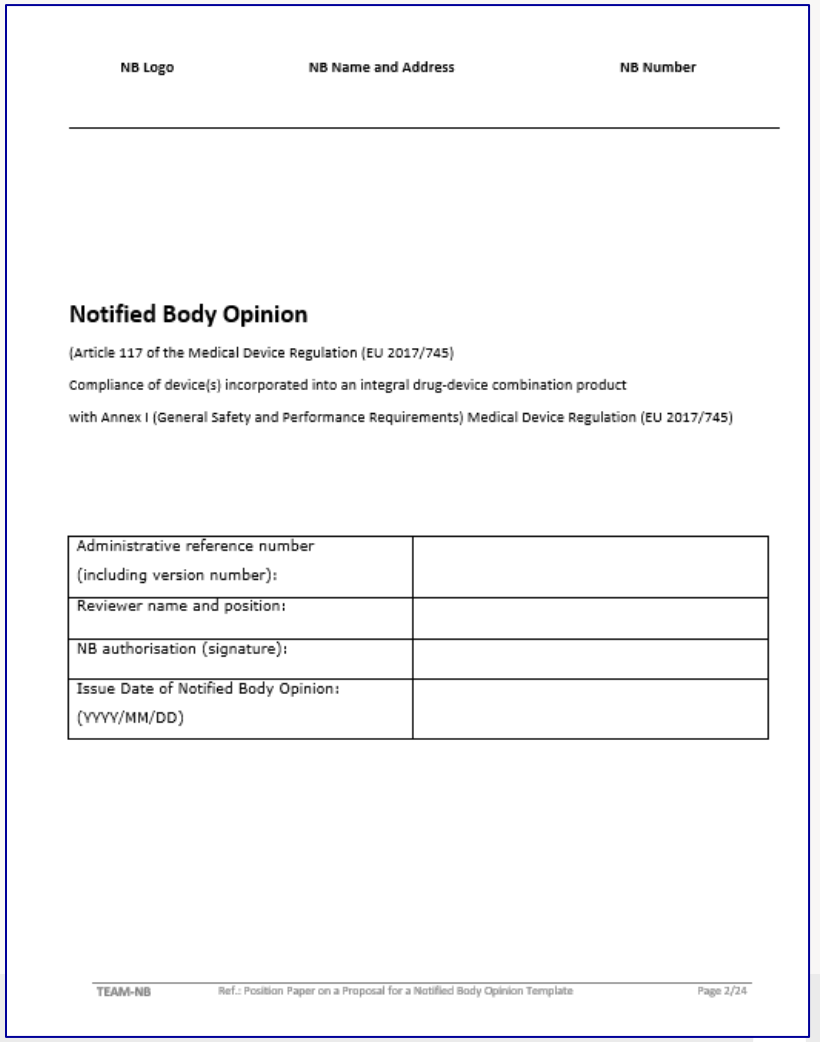
Documentation Learning Points- Example



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



NB Logo NB Name and Address NB Number

Notified Body Opinion

(Article 117 of the Medical Device Regulation (EU 2017/745)

Compliance of device(s) incorporated into an integral drug-device combination product

with Annex I (General Safety and Performance Requirements) Medical Device Regulation (EU 2017/745)

Administrative reference number (including version number):	
Reviewer name and position:	
NB authorisation (signature):	
Issue Date of Notified Body Opinion: (YYYY/MM/DD)	

TEAM-NB Ref.: Position Paper on a Proposal for a Notified Body Opinion Template Page 2/24

Notified Body Opinion- version 1

- Detailed review of GSPRs shared with Competent Authority
  - Partial compliance an option

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

NBOp- Future version

1.1. Summary of Notified Body Opinion

The technical documentation for <medicinal product> was reviewed in accordance with Annex I of Regulation 2017/745. The assessment has been performed for the purpose of < *initial application / variation application* >. *In the case of variation assessment:* Previous results <*have been considered as documented in XXXX / have not been considered*>.

The objectives of this assessment were found to have been met/ not met for the applicable GSPRs.

GSPR Chapter	Assessment	
The device conforms to the relevant **General Requirements** as outlined in **Chapter I** of Annex I of Regulation (EU) 2017/745	☐ Yes	☐ No
The device conforms to the relevant **Requirements regarding Design and Manufacture** as outlined in **Chapter II** of Annex I of Regulation (EU) 2017/745	☐ Yes	☐ No
The device conforms to the **relevant Requirements regarding the Information supplied with the Device** as outlined in **Chapter III** of Annex I of Regulation (EU) 2017/745	☐ Yes	☐ No

A detailed summary of this technical documentation assessment is presented in sections 2 – 3 of this report below.

Conformity to the relevant GSPRs has been assessed. Non-applicable GSPR have been identified and sufficiently justified. Conformity with the following GSPRs are not fully met and rational for non-compliance is provided in section <*XXX*>.

The Notified Body retains the technical documentation submitted by the manufacturer and related correspondence.

3.1. Solutions adopted to fulfil the GSPRs

Note this section is to provide a summary of the aspects reviewed per GSPR. Briefly describe the solutions adopted relevant to the GSPRs and the NB review, highlighting any areas of concern, even if the overall opinion is positive, for example biocompatibility can be demonstrated but ISO 10993-01:2019 not followed.

3.1.1. Design and Manufacturing Information

<To cover GSPRs 1,4,7,8,11 to include process flow and locations packaging and sterility aspects

3.1.2. Design Validation

<e.g. human factors studies, GSPR 1,6,11. To include packaging and sterility aspects>

3.1.3. Benefit-Risk Analysis and Risk Management

<Short summary and conclusions to cover GSPR 1,2,3,4,5,8>

3.1.4. Biocompatibility

<GSPR 10 including CMR or endocrine disrupting substances>

3.1.5. Stability and Shelf Life

<GSPR 7>

3.1.6. Labelling and Leaflet

<to confirm the aspects of labelling that have been reviewed as part of the NB review for example output from risk assessment or instructions for use of the device part, GSPR 23>
<The headings below can be deleted if not relevant to the medicinal product in question>

3.1.7. Tissues/cells of human or animal origin

<GSPR 13>

3.1.8. Connection to other devices

<GSPR 14.1>

3.1.9. Measuring Function

<GSPR 15>

3.1.10. Electrical Safety, Software and EMC

<GSPR 17,18,19>

3.1.11. Protection from radiation, mechanical and thermal risks, and risks posed to the patient or user by devices supplying energy or substances

<GSPR 16, 20 and 21>

3.2. Recommendations to the Competent Authority

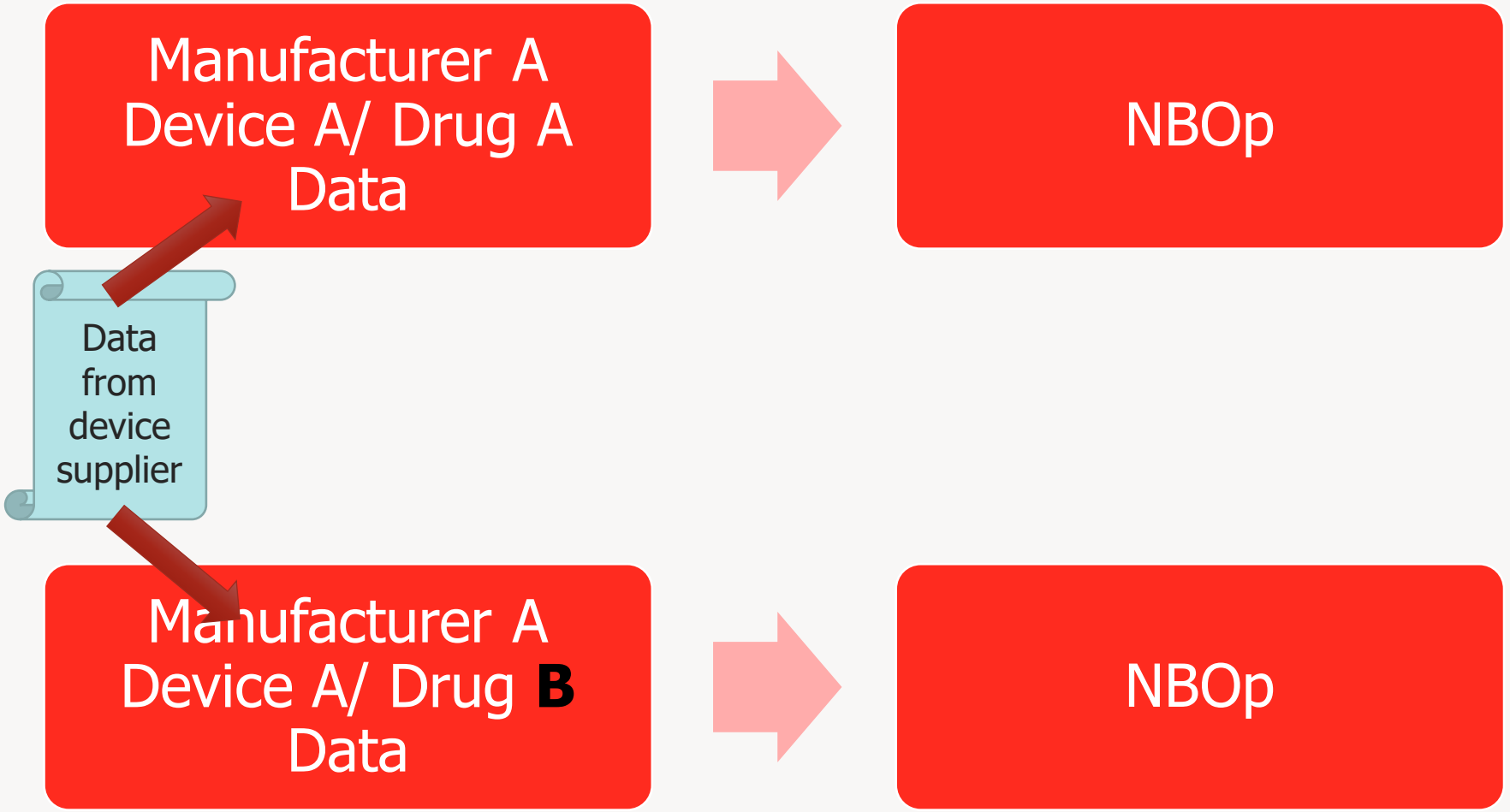
Summary of any concerns or elements for follow up. If full shelf life data, for example, has not been reviewed an instruction that the NB needs to review or the Competent Authority don't need the NB to review the full data.

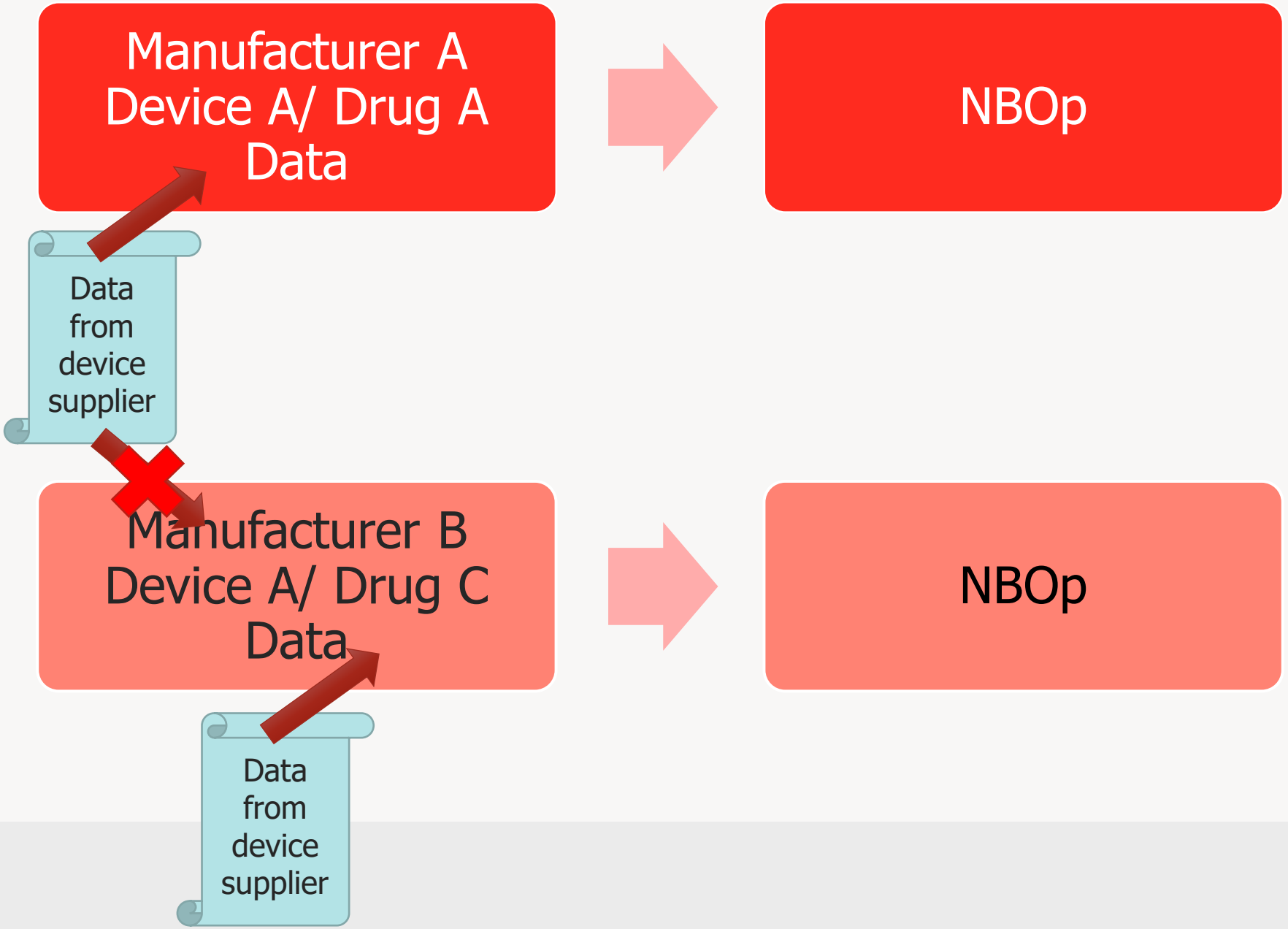
Challenges

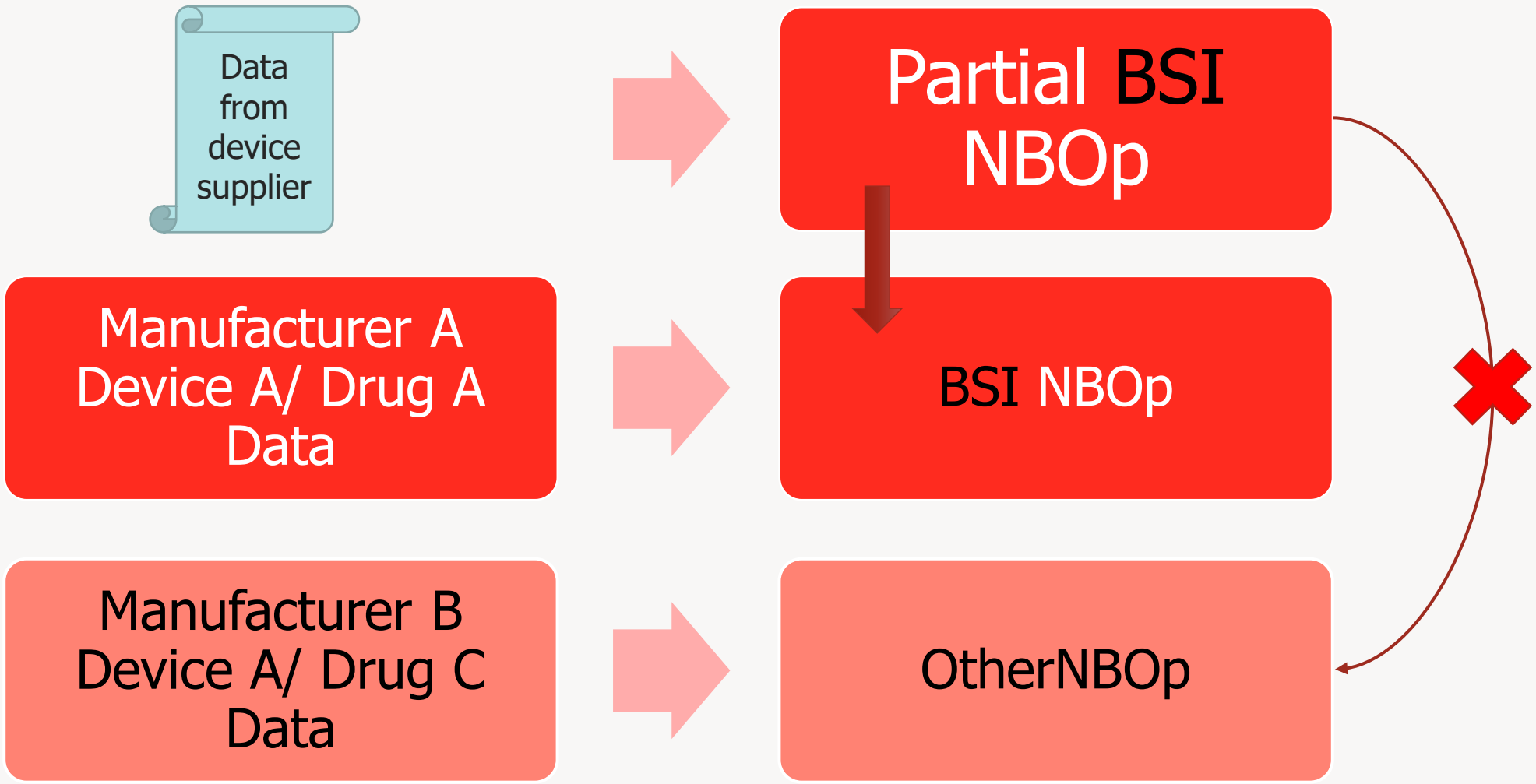
How will NBOp be used?	▪ Are the CAs looking for information in the NBOp or just that assessment is complete
Responsibility where there is overlap	▪ Sterilisation- particularly components and re-sterilisation. EP specification. ▪ Shelf life
What to do about incomplete data	▪ eg stability/ transport studies, draft SPC ▪ Does competent authorities accept the submission of the NBOp during the clock stop?
What to handle non-fulfilled requirements?	▪ Missing evidence for an GSRP → Negative Opinion ▪ Follow up actions? Recommendations to the CA.

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 but no general process







Team NB – European Association for Medical devices of Notified Bodies

26 members from 15 countries (status per Oct. 2019)

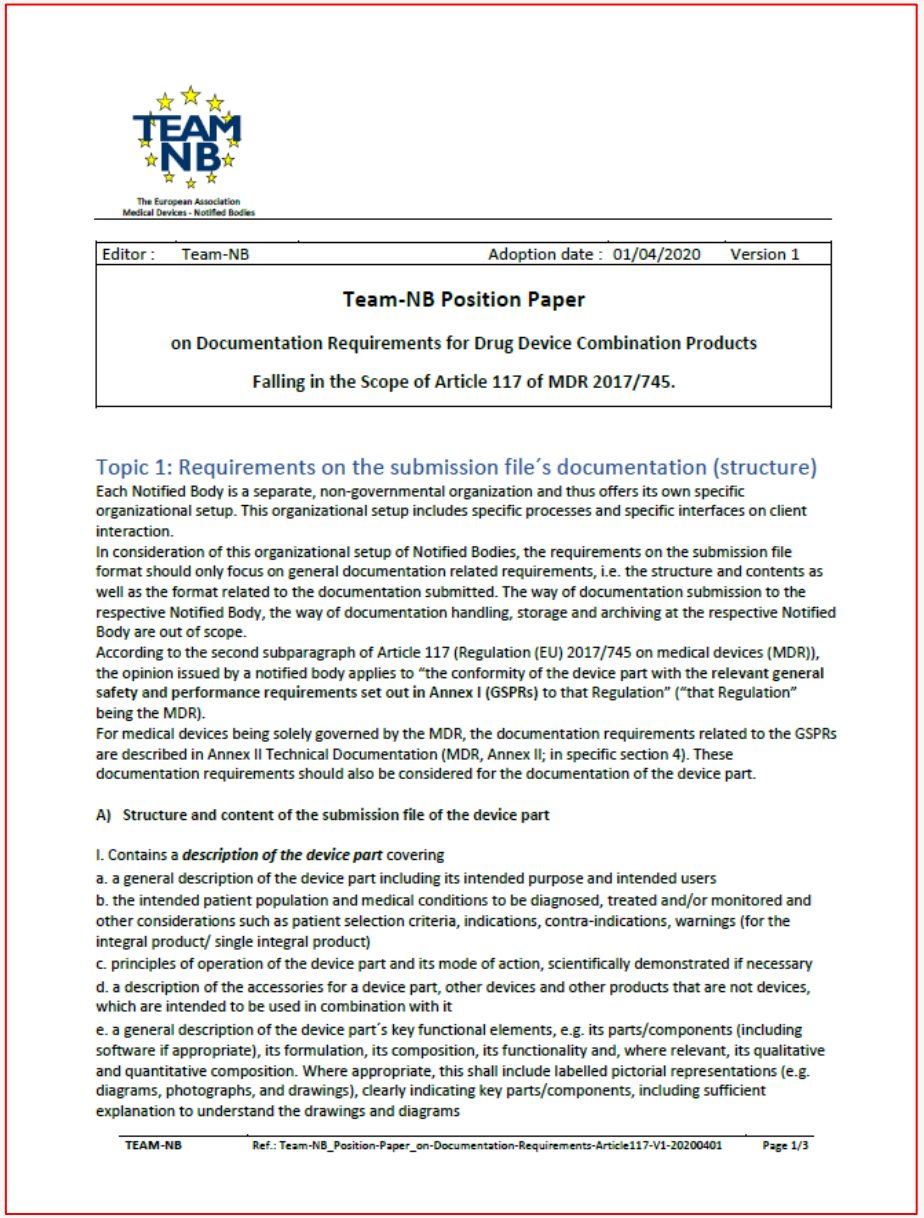
Aims:	Contribute to notified bodies working in a harmonized way
	Communication with EU Commission, Competent Authorities, Industry
	Represent notified bodies

Working groups to support its members
Article 117 working group exists since May 2020

Documentation Guidance

- Agreed by Team-NB
- Documentation requirements for DDCs
- = Requirements for Annex I

- Not the only source of information on this topic!



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Editor: Françoise SCHLEMMER	Date: December 2020
Position paper for the interpretation of device related changes in relation to a Notified Body Opinion as required under Article 117 of Medical Device Regulation (EU)2017/745	

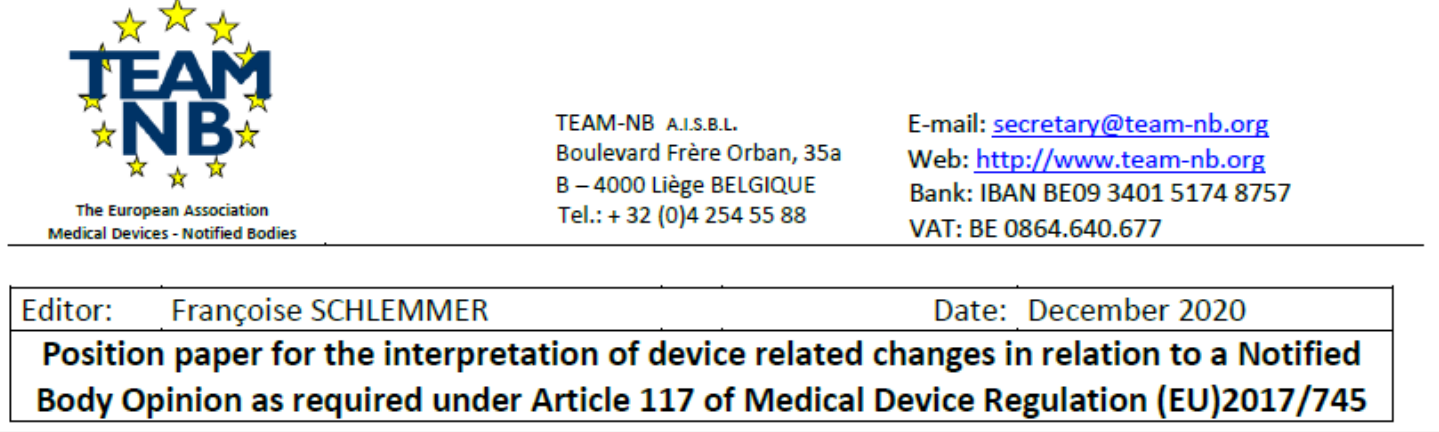
Intended to be a discussion of device related changes which will potentially require a new or revised NBOp

To create alignment between Notified Bodies on interpretation of substantial changes

Based on existing NBOG best practice guide, MDCG guidance 2020-3 and ISO 20069

- **NOT intended to provide any position on submission of a variation and type of variation**

Team-NB Position Paper



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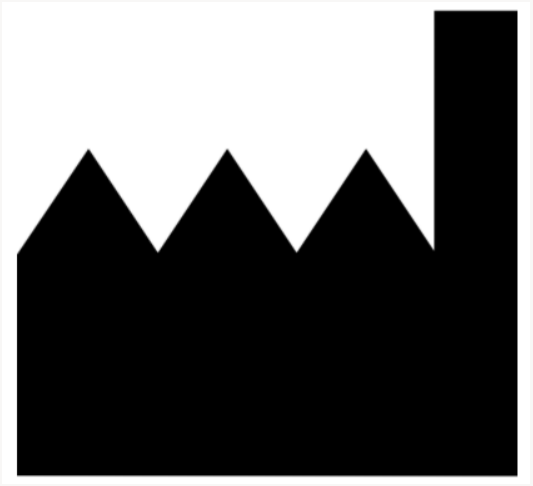
- Team-NB received comments from EMA/NCA
- Draft position paper provided to industry participants of EMA workshop
- Upon completion and agreement by NB's, the paper was be published as Team-NB position paper
- https://www.team-nb.org/wp-content/uploads/2020/12/Team-NBPosition-Paper-Art117SubChangeLifeCycleMngt-202012.pdf

Collaborative



Thank you!

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.

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