Notified body experience with NBOps

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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 Devices Medicinal and Biologics team combined experience 107 YEARS

Team expertise

- Antibacterial envelopes
- Human serum albumin
- Chondroitin sulphate
- Haemostats
- Sutures
- Inhaled drug products
- Collagen
- Soft tissue repair
- Vitrification systems
- Organ preservation solutions
- Drug eluting stents
- Tissue engineering
- Formulation development
- Pericardium
- Gelatin
- Cartilage repair devices
- Pericardium

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
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

Regulatory Path

- Principal Mode of Action (PMOA) informs Regulatory Path
- Immunological
- Metabolic
- Pharmacological

Yes; provide cert

MAA

Device Part CE Marked?

No

Notified Body Opinion

Notified Body Opinion: Only required where the device would require Notified Body Conformity Assessment if placed on market as a standalone

- Class 1s/mf
- Class IIA
- Class IIB
- Class III

(EU) 2017/745

90/385/EEC (AIMDD)

CE
Notified Body Assessment: Article 117

BSI Review Process:
Similar to Design Dossier Review- minus QMS and clinical

- Quotation processed & contract review
- Technical documentation provided
- BSI technical assessment
- Responses & questions cycle
- Closeout of questions based on technical specialist recommendation
- Certificate decision (independent review)
- Summary document / report issued to manufacturer
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...
Guidance

MDR Documentation Submissions
Best Practices Guidelines

..making excellence a habit..
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
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

MAA risk management process

- Component risk assessment
- Device supplier risk assessment
- Drug/ Device Combination risk assessment
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
### Notified Body Opinion - version 1

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

<table>
<thead>
<tr>
<th>18.8</th>
<th>Design &amp; manufacture – avoid unauthorized access</th>
<th>☑️YES ☐NO ☐PARTIAL</th>
<th>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.</th>
</tr>
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<tbody>
<tr>
<td>19.1</td>
<td>Active implantable devices – reduce risks as far as possible connected with use of energy sources, medical treatment, where maintenance and calibration are impossible</td>
<td>☐YES ☑NO ☐PARTIAL ☑N/A</td>
<td>N/A – appropriate rationale given</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>GSPR Chapter</th>
<th>Assessment</th>
</tr>
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<tbody>
<tr>
<td>The device conforms to the relevant General Requirements as outlined in Chapter I of Annex I of Regulation (EU) 2017/745</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>The device conforms to the relevant Requirements regarding Design and Manufacture as outlined in Chapter II of Annex I of Regulation (EU) 2017/745</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>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</td>
<td>□ Yes □ No</td>
</tr>
</tbody>
</table>

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 GSPRs have been identified and sufficiently justified. Conformity with the following GSPRs are not fully met and rational for non-compliance is provided in section <XX>.

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 GSPR 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 1,2,3,4,5,8,9>

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 NB assessment or instructions for use of the device part, GSPR 23.>

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 contents 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
Data from device supplier

Manufacturer A Device A/ Drug A Data

NBOp

Manufacturer A Device A/ Drug B Data

NBOp
Manufacturer A
Device A/ Drug A
Data

Data from device supplier

Manufacturer B
Device A/ Drug C
Data

Data from device supplier

NBOp

NBOp
Data from device supplier

Manufacturer A
Device A/ Drug A Data

BSI NBOp

Manufacturer B
Device A/ Drug C Data

Partial BSI NBOp

OtherNBOp

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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!
Team-NB Position Paper

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.

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

Based on existing NBOG best practice guide, MDCG guidance 2020-3 and ISO 20069.
Team-NB Position Paper

- 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
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.