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

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

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

10,000+ in the Americas

47,000+ in EMEA

25,000+ in APAC

53% of the Fortune 500

83% of the FTSE 100

80% of the NIKKEI 225
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
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
Who is involved in the Article 117 Process

- EU Commission
- Competent Authorities
- Manufacturers
- Notified Bodies

The players
Article 117
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

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.

* See EU Regulation (EU) 2017/745 on medical devices.
Drug Device Combinations - Single integral, exclusively for use, not reusable

- Example DDCs in scope

- Not in scope
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

Medicinal Product

Immunological Metabolic Pharmacological

PMOA

In cases of Doubt Art. 2.2 (MPD)

Relevant Essential Requirements of Annex I of MDD /AIMD apply

2001/83/EC (MPD)

MAA

93/42/EEC (MDD)

90/385/EEC (AIMDD)

CE

Credit: Paul Scannell, from TOPRA 2019
Future Process for Drug Device Combinations - Under MDR

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

TO-BE PROCESS (from 26 May 2021)

Regulatory Path:
- Principal Mode of Action (PMOA) informs Regulatory Path

Immunological Metabolic Pharmacological

Medical Product

PMOA

Medical Device

Mechanical Physical

In cases of Doubt Art. 2.5 (MPD)

2001/83/EC (MPD)

Device Part CE Marked?

Yes: provide cert

MAA

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
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)

- 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
Estimated timeline for Article 117 reviews

Pre-review tasks
- Application submission
- Quote issued and signed
- Contract review completed
- Scheduling
- Complete documentation submission
- Documentation completeness check

Medicinal review conducted: NBoP summary passed on to technical specialists

Working days
BSI timeline by task 20
Total BSI timeline 20

Working days
BSI timeline by task 20
Total BSI timeline 60

BSI 1st review round and questions sent to client

BSI 2nd review round and questions sent to client

Client responds to BSI

Clock stops

BSI 3rd review round and questions sent to client

Working days
BSI timeline by task 10
Total BSI timeline 70

Client responds to BSI

Clock stops

Working days
BSI timeline by task 10
Total BSI timeline 80

Final BSI NBoP report issued to client

BSI finalizes NBoP Report and makes submission for decision making
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

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.

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.
## Notified Body Opinion

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<td></td>
<td><strong>Design &amp; manufacture – avoid unauthorized access</strong></td>
<td><strong>YES</strong></td>
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<td></td>
<td>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.</td>
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<tr>
<td></td>
<td><strong>Active implantable devices – reduce risks as far as possible connected with use of energy sources, medical treatment, where maintenance and calibration are impossible</strong></td>
<td><strong>YES</strong></td>
</tr>
<tr>
<td></td>
<td>N/A – appropriate rationale given</td>
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bsi.
Article 117 – Guidance

- Current Guidance
- Areas where further guidance is needed
  - Classification
  - Platforms
  - Changes
Guideline on the quality requirements for drug-device combinations
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

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<th>Type of integral device included in the MAA</th>
<th>New submissions as of 26th May 2020</th>
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<tr>
<td>Class I (sterile, measuring or reusable surgical instrument*)</td>
<td>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</td>
</tr>
<tr>
<td>Class IIa, Class IIb, Class III</td>
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<tr>
<td>Class I (non-sterile, non-measuring, or non-reusable surgical instrument)</td>
<td>The marketing authorisation dossier should include a Declaration of Conformity for the medical device, where available.</td>
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* 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.