HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

The Notified Body Opinion

An assessor's view

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Disclaimer

The contents of this presentation are personal observations and are not necessarily representative of the HPRA, EMA or any other agency

Regulation 2017/745

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.

Applicant shall provide an opinion on the conformity of the device part with the relevant GSPRs as set out in Annex I **- NBOp**

Medicines Authority - Assessor Remit

- In accordance with Directive 2001/83/EC – assessment of any risk relating to quality, safety or efficacy of the medicinal product
- As per draft guideline (EMA/CHMP/QWP/BWP/259165/2019):

  "The assessment of the suitability of a device for its intended purpose should take into account the relevant quality aspects of the device itself and the context of its use with the medicinal product"

  "Complexity of the device, patient characteristics, user requirements, clinical setting/ use environment"

- Aim to

a) Ensure the B/R (Q/S/E) of the finished medicinal product is positive

b) Minimise duplication of effort for regulatory authority/ notified body/ applicants

What we suggested:

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Annex 2: Template cover sheet for Notified Body Opinion

It is intended that this document is completed to provide information on the medicinal product containing an integral medical device. Where an application is made for a DDC containing an individual device part, the applicant or MAH completes this section.

GENERAL INFORMATION

PRODUCT DETAILS	
Invented / Trade name of the medicinal product	<as per MAA>
Applicant	<Name and address of MAH i.e. legal entity holding the MA>
Marketing authorisation type	<e.g. Centralised application>
Marketing authorisation procedure number	<e.g. EU/xxx/xxx.>
Pharmaco-therapeutic group (ATC code)	<e.g. D08A C52>
Indication(s)	<As per SPC4.1>
Pharmaceutical form(s) and strength(s)	<e.g. 10mg, 20mg [illegible] for injection, pre-filled syringe>
INN (or common name) of the active substance(s):	<as per MAA>
Authorisation to use NB's [illegible]	<Suitably authorised / signed by the MAH*

Annex 3: Suggested template for Notified Body Opinion*

Date
Version Number

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: _____

Authorised by (name): _____

Authorised by (signature): _____

Issue date (YYYY/MM/DD): _____

* This is a suggested template, to facilitate ease of review by the Competent Authority; others can be used

What we received (based on sample, n = 4)

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Product 1 – Medicinal product dossier overview (eCTD)

Product 1 – Biological (NAS) in PFS, combined with either safety syringe (SS) or auto-injector (AI)

Location of device information within the dossier

- 3.2.P.1 – brief description
- 3.2.P.2 - design verification of devices as per ISO, design validation including summary of HF studies, clinical studies
- 3.2.P.3 – assembly process and controls
- 3.2.P.5 – device-specific specifications
- 3.2.P.7 – diagrams, material of construction, critical material attributes
- 3.2.P.8 – long-term and accelerated study results and protocols
- 3.2.R – Human Factors and clinical study summary, NBOp for SS and for AI

Product 1 - NBOp

- Two NBOps (SS and AI) each< 30 pages
- Did not use EMA draft template
- Clearly stated MAH, product, internal reference number
- Overall conclusion clearly stated – met requirements of Article 117, reviewed technical documentation against Annex I of Reg (EU) 2017/745
- Includes general description aligned with module 3, intended purpose of DDC aligned with SPC, assessment of GSPRs (tabular format, clearly highlights yes/no/partial/na and brief summary of the data reviewed and overall conclusion

13.2	Devices manufactured utilising tissues or cells, or their derivatives, of animal origin	☒YES ☐NO ☐PARTIAL	TSE statements confirm that the processing conditions defined in EMEA 410/01 rev 03 have been met

Product 2 – Medicinal product dossier overview (eCTD)

- MAb (biosimilar) in PFS, assembled with SS or AI

Location of device information within the dossier

- 3.2.P.1 – brief description
- 3.2.P.2 - design verification plan and verification report, scale up, transport
- 3.2.P.3 – assembly process and controls, definition of batch size
- 3.2.P.5 – device-specific specifications
- 3.2.P.7 – diagrams, material of construction, specifications
- 3.2.P.8 – based on primary container closure
- 3.2.R – NBOp for SS and for AI, device RMP, URRA, threshold analysis
- Module 2.5 and 2.7 – HF and Usability studies
- 1 x NBOp under MDR, 1 x ER checklist and design file under MDD – not required at present

Product 2 - NBOp

- ~ 30 pages
- Did not use EMA draft template
- Clearly stated MAH, product, internal reference number
- Introduction clearly identified GSPRs which could not be confirmed – gaps were identified and highlighted to CA where information had not been provided, useful for targeted assessment
- Body of report – product description, purpose of DDC, therapeutic context, list of GSPRs in tabular format

7	Design & manufacture – transport, storage	☐YES ☒NO ☐PARTIAL	Transit studies have not been completed and therefore documentation was not available to demonstrate the suitability of the packaging for transport.

Product 3 - Medicinal product dossier overview (eCTD)

- MAb (line extension) in PFS assembled with NSP device or AI

Location of device information within the dossier

- 3.2.P.1 – brief description
- 3.2.P.2 – RMP, design verification plan report, design validation and HF program, bridging clinical to commercial
- 3.2.P.3 – assembly process and controls
- 3.2.P.5 – device-specific specifications,
- 3.2.P.7 – technical drawings, material of construction, specifications
- 3.2.P.8 – platform approach to stability
- 3.2.R – certificates of conformance, GSPRs assessment by MAH for NSP-PFS & AI, NBOp for PFS
- Module 5.3 Other studies – HF engineering and HF summary reports

Product 3 - NBOp

- Two NBOps (80+, 100+ pages)
- Did not use EMA draft template
- Clearly stated MAH, product, EU number, internal ref number
- Overall conclusion clearly stated

The device conforms to the relevant **General Requirements** as outlined in **Chapter I** of Annex I of Regulation (EU) 2017/745	☒ Yes	☐ No	☐ Partially
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	☐ Partially
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	☐ Partially

- Includes general description aligned with module 3, intended purpose of DDC aligned with SPC, classification of device, assessment of GSPRs (tabular format, clearly highlights yes/no/partial and brief summary of the data reviewed and overall conclusion

Summary of NBOp differences

	NBOp 1	NBOp 2	NBOp 3	NBOp 4
Length	< 30 pages	30+ pages	80+ pages	120 +pages
MAH, product name, reference number	√	√	√	√
Description aligned with M3	√	X	√	√
Intended purpose aligned with SPC	√	X	√	√
Device classification	X	X	√	√
Alignment with GSPRs		X	√	√
Clear opinion	√	√	√	√
List of standards	√	√	X	X
Summary of risk assessment	X	X	√	√

Key take home messages

For MAH

- Include relevant information in dossier, consistent with draft guideline
- Clearly cross reference to other sections of module 3/ other sections of dossier for ease of review e.g. location of HF study

For NB in NBOp

- Clear conclusions at beginning, highlight areas which were not assessed/ not met which should be focused on during MAA
- Consistency between NBOp and dossier/ SPC
- GSPRs in tabular format with explanation for decision
- Medical device classification is useful

Conclusion

- If MAH has clearly presented device data in the dossier

  AND

- Conclusions of NBOp are clearly outlined

  THEN

- Very little overlap/duplication of effort
- Assessors cross-check device details match SPC/ dossier,
- Assess information relevant to device in combination with the medicinal product
- Focus on gaps identified/ non-conformance with GSPRs