The European Association of Medical devices Notified Bodies

Team-NB Position Paper

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Best Practice Guidance for the Submission of Technical Documentation under Annex II and III of Medical Device Regulation (EU) 2017/745

Information to be supplied by the manufacturer –

a collaborative notified body approach.

The European Association of Medical devices Notified Bodies

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Contents

Scope of Document

This best practice guidance document has been developed by members of Team NB who have reviewed the best practice guidance documents submitted by individual Team NB notified body members, with the purpose to develop a unified approach on the expectations of technical documentation submissions from manufacturers.

This technical documentation submission guidance is aligned to the requirements of Medical Devices Regulation [MDR] (EU) 2017/745, described in detail in Annexes II and III of Regulation (EU) 2017/745.

Disclaimer:
The content of the best practice guidance is based on the interpretation of the Medical Device Regulation EU 2017/745 by Team NB and affiliated notified bodies. During a technical documentation assessment, it may be required that additional documentation/information may be needed to be submitted as part of the technical assessment that goes beyond what is listed in this guidance document, and each notified body reserves the right to request additional information.

This guidance is intended to be comprehensive, but not exhaustive in its request.

General Considerations

The most common reasons for delays in Technical Documentation reviews by notified bodies are:

- **Incomplete Submissions** – Insufficient or missing information not provided that is required for the conformity assessment activities.

- **Lack of Cohesive Structure of Technical Documentation** - The information is presented within the Technical Documentation but is difficult to locate.

To avoid delays and to further improve your submission, please consider the following practical points:

<u>Communication with the notified body before an application is lodged</u>

- ✓ Manufacturers should contact their notified body to clarify the language requirements for the technical documentation submission of the individual notified body as mentioned in the MDR, per Article 52 (12).
- ✓ Manufacturers should also contact their notified body to clarify the requirements related to documentation labelling and methods for submission to the notified body.

Technical documentation submission

- ✓ Where appropriate the most recently updated comprehensive reports and data should be included. Abbreviated or partial test reports are not considered acceptable.
- ✓ Verification reports provided should be complete, i.e. not a report with subsequent amendments or revisions as the device was changed.
- ✓ The technical documentation shall document how the manufacturer ensures compliance to every applicable GSPR.
- ✓ There are many areas of the technical documentation that will require the duplication of information for multiple documents such as device description. Please ensure that the information is correct throughout all areas where this information is duplicated and consider the risk of potential errors/inconsistencies when updating (e.g. Basic UDI-DI, UDI-DI, intended use, indications for use, contraindications, warnings, etc.).
- ✓ Ensure the data in the technical documentation is consistent with the data provided in the respective application forms.
- ✓ Valid justifications should always be provided or accompanied where there are deficiencies in the requested data.

As part of the technical documentation assessment, please be aware that there are multiple individuals from the notified body involved in the review and therefore you may be requested to provide duplication of documents.

Leveraging of evidence from past Directive assessments

For certain classifications of medical devices, the MDR requires that manufacturers submit an initial application for certification under MDR to notified bodies (NBs). NBs are required to undertake the applicable conformity assessment activities, typically a combination of quality management system audits and technical documentation assessments to verify compliance to the MDR requirements before certification can be granted. For certain areas where the requirements have not change significantly between the Directives and the MDR, and the evidence provided by the manufacturer to meet such requirements has not changed, NBs may be able to leverage/utilise past NB assessments carried out under the Directives to establish compliance of the MDR requirements without having to re-evaluate the evidence. Such an approach could help avoid duplication and reduce the durations of the NB MDR conformity assessment activities and hence contribute to faster transition of medical devices from the Directives to the MDR.

It is important to note that the manufacturer should continue to provide full technical documentation in line with Annex II and Annex III of the MDR. However, it would aid the NB technical documentation assessment process if manufacturers clearly indicate whether the evidence/data they have submitted as part of an MDR application (or technical documentation) has changed or not; the extent of changes compared to what may have been previously reviewed/assessed by their notified body (this may be provided separately or included in the GSPR checklist) under the Directives; and references to NB reports where such evidence was previously assessed.

Next Revision Date: (2 years from endorsement)

This document is subject to further revisions as experiences will be gained.

This document is the result of a huge initiative to compile existing guidance from many notified bodies, to harmonise expectations and facilitate manufacturer's tasks when drafting their technical documentation.

Team NB may decide to revise this document to adapt it to changes in the regulation, development of guidance documents (e.g. MDCG documents) and the change in interpretation over time.

Device Description & Specifications - Including Variants, Accessories, Classification & Materials

Please ensure that the product name, intended purpose/intended use is consistent throughout the different evidentiary documents. If not, please provide an explanation within the main technical document describing the differences and how they would still be applicable to the name/intended use being reviewed under the MDR.

1. Device description and specification details should include:

(a) product or trade name and a general description of the device including its intended purpose and intended users.

- Applicable NBOG codes (MDA/MDN, MDS, MDT) as well as information whether device is for single use only, multiple use, reprocessing and its number of cycles shall be included.
- The general device description should enable understanding of the design, packaging, sterilisation, or other characteristics of the device.
- Sufficient information should be provided to understand the intended purpose of different design features.
- The intended purpose or intended use should provide enough detail to explain the disease conditions the device is intended to treat or monitor.
- The intended users of the device (i.e. medical professionals in a specialty, clinical nurses, lay-persons, etc.) shall be identified.

(b) the Basic UDI-DI as referred to in Part C of Annex VI assigned by the manufacturer to the device in question, as soon as identification of this device becomes based on a UDI system, or otherwise a clear identification by means of product code, catalogue number or other unambiguous reference allowing traceability.

- Clear identification of device by unambiguous reference, allowing traceability (Basic UDI-DI), together with other traceable reference number (e.g. product code, catalogue number, etc.).
- Information to be consistent also with the information on the labelling.

(c) 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.

- The Technical Documentation shall include intended patient population (including intended parts of the body or type of tissue applied to or interacted with) and medical conditions to be diagnosed, treated and/or monitored and other considerations such as patient selection criteria, indications, contra-indications and warnings, intended conditions of use (environment, frequency, location, mobility).

(d) principles of operation of the device and its mode of action, scientifically demonstrated if necessary.

(e) the rationale for the qualification of the product as a device.

- Per MDR, Article 2, please explain how the product qualifies as a medical device. Or explain if it is a product without an intended medical purpose (Annex XVI). Please note this is different from the classification of the device per MDR Annex VIII.

(f) the risk class of the device and the justification for the classification rule(s) applied in accordance with Annex VIII.

- Please indicate the device classification and rationale per MDR Annex VIII. The rationale should address each point of the selected classification rule. If multiple classification rules apply, all should be identified and the strictest rules resulting in the higher classification shall apply.

- If the device contains multiple components that on their own might be classed differently, please note the higher classification shall apply.

- If the device is a Well-Established Technology (WET) as per Articles 52.4 and 52.5 of MDR, a rationale supporting the determination of the device as a WET should be included considering any published guidance available on such devices.

(g) an explanation of any novel features.

- A description of novel features of the device needs to be provided as part of the device description/specification section.

- Please explain whether novel features are novel in comparison to other devices in the market and/or novel in comparison to other devices of the manufacturer.

- Novel features must be accompanied by scientific evidence, e.g. from clinical investigations. Novel features might require a clinical investigation also in the case of Class IIa or IIb devices.

- The degree to which the device is innovative may be defined based on the criteria given in the ANSM 'Degrees of novelty card'. The impact of this novel feature on the technical or clinical safety and performance of the device shall be briefly described here with reference to the detailed verification/validation studies.

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

- The following information should be provided for any accessories (including Class I) associated with the device:

  - Brief description of the accessory/accessories and how they are used with the device(s).
  - Classification of the accessories and rationale for classification.
  - Technical Documentation references (file name, issue status, date). Indicate clearly if the accessories are packaged with the device or provided separately or both. Also clarify if the accessories are already certified and if yes, provide the certificate references.

  Please note evidence should also be provided within the Technical Documentation to demonstrate compatibility of the devices with any applicable accessories. The Technical Documentation should identify any accessories which are not included with the device, but which are necessary for its use.

(i) a description or complete list of the various configurations/variants of the device that are intended to be made available on the market.

- All configurations/variants of the product covered by the Technical Documentation need to be clearly identified.

- Please provide sufficient information to distinguish different variants of the device.

(j) a general description of the 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.

- General description of the 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 shall be included. 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.

- Critical aspects of the specifications including tolerances should be included. This may consist of Critical to Quality aspects, critical dimensions, and a list of critical components/ingredients shall be provided.

- For active medical devices, electrical circuit diagrams shall be a part of the Technical Documentation and should enable the reviewer to understand the electrical safety concept and identification of all relevant electrical components.

Note: This is important for pre-clinical aspects, such as safety concepts, risk management aspects, testing of e.g. physical/mechanical/electrical properties etc., compatibility with other products/accessories, etc. as well as clinical aspects.

(k) a description of the raw materials incorporated into key functional elements and those making either direct contact with the human body or indirect contact with the body, e.g., during extracorporeal circulation of body fluids.

- The Technical Documentation should identify the raw materials incorporated into key functional elements of the device including information on any coatings that are critical for device safety and performance. The nature of contact with the human body (e.g. direct or indirect contact, contact with circulating body fluids, etc.) should be clearly identified. The submission should clearly indicate whether the device utilises or is used in conjunction with any human or animal- based products or other non-viable biological substances. Materials which are or include derivatives of human or animal origin should be clearly identified. Please identify if the device contains nanomaterials. The technical documentation should also identify the raw materials used in the packaging of the device, including primary and secondary packaging. Submission should include the device Bill of Materials.

(l) technical specifications, such as features, dimensions and performance attributes, of the device and any variants/configurations and accessories that would typically appear in the product specification made available to the user, for example in brochures, catalogues and similar publications.

- Complete technical specifications for the device and any variants/configurations, including indication of which of these are presented in the product specification made available to the user.

2. Reference to previous and similar generations of the device

(a) an overview of the previous generation or generations of the device produced by the manufacturer, where such devices exist.

- All submissions should be accompanied by a market history to enable an understanding of the context of device development.

- If the device is new and has never been marketed by the manufacturer anywhere in the world, please state this explicitly.

For existing devices:

- Ensure that a market history is provided indicating the nature and timing of any changes and that any associated documents (i.e. risk analyses, labelling, clinical evaluation reports, verification / validation data, etc.) account for these changes.
- Provide evidence (e.g., NB Reference numbers of previous reviews) to demonstrate that NB has been notified of all significant changes (if applicable).
- For initial applications under MDR, please confirm whether the device has been previously marketed under MDD and whether any changes have been made in comparison to the MDD-certified device.
- Market history should include EU and approvals in other geographies, including sales volumes per country.
- If the device is a system, ensure that the number of units sold is broken down by device component and per year.

(b) an overview of identified similar devices available on the Union or international markets, where such devices exist.

- Provide an overview of identified similar devices available on the EU or international markets if such devices exist. This shall include a comparison of these devices with the device under review to show the similarities and differences.

Information to be supplied by manufacturer (Includes Declaration of Conformity, Labelling, IFU, Implant Card, Surgical Technique brochure etc.)

Labelling

Please provide the label or labels on the medical device, in the languages accepted in the Member States where the device is envisaged to be sold. This includes Device or Product labelling, Sterile packaging labelling, Single unit packaging labelling, Sales packaging labelling, Transport packaging labelling.

Medical devices generally use multiple levels of labelling, and it is recognised that not all devices may have the different levels of packaging specified in this section or different terms may be used than those specified here. Legible versions of all applicable levels of labels should be provided (e.g. secondary pack, primary pack) and should be representative of the finished form, showing all included symbols.

If possible, provide drawings with the packaging configuration (showing placement of all labels) and label specifications (layout, size).

The position of labels on the finished product should be clear. If the device has a sterile package, clearly identify the label for the sterile package. If any of the packaging is printed with information for the user (including pictures / schematics of the device) this should also be provided.

Verification of label contents must be carried out in accordance with GSPR 23. For Class IIa and IIb medical devices, there is a commitment by the Manufacturer to apply UDI carriers on the device label, starting from May 2023. For Class Is devices, there is a commitment by the Manufacturer to affix the UDI carriers on the device label, starting from May 2025.

Please ensure that any specific requirements of relevant harmonised standards or Common Specification (CS) are addressed in the labels and information for use.

Instructions for use/Device Operating Manual(s)

Please provide the instructions for use (IFU), in the languages accepted in the Member States where the device is envisaged to be sold. Manufacturers must ensure that the information within the IFUs, especially related to intended purpose, indications, contra-indications, and other safety related information such as side effects, warnings is aligned with similar information from other sections such as risk management, clinical evaluation, usability, pre-clinical performance data etc.

IFUs must contain all the information required as per applicable requirements specified within GSPR 23.

Please ensure that any specific requirements of relevant standards or CS are addressed by the instructions for use. For example EN 60601-1, EN 60601-1-X, EN 60601-2-X, EN ISO 17664, EN ISO 14630 have specific requirements for the Instructions for Use.

Please provide surgical technique, user manual, installation and service manuals if applicable.

For devices provided without an IFU/Leaflet/Instructions, provide the information detailed in GSPR 23.4(p) and 23.4(v).

Electronic IFU (e-IFU) information (if applicable, and as per (EU) 2021/2226)

If electronic IFU will be utilised, ensure compliance has been clearly outlined and evidence included to demonstrate compliance with all relevant aspects of Regulation 2021/2226. E-labelling information as provided on the device or on a leaflet. Provide documented risk assessment covering the elements as required by the e-labelling regulation.

Patient handbook

Some devices incorporate all the information relevant for the patient/user within the IFU itself. Some devices are accompanied by a patient handbook with additional instructions specific to the patient, for example with devices (or parts, components of the devices) that are patient operated. If the device

is supplied with a patient handbook, this should be provided in the languages accepted in the Member States where the device is envisaged to be sold.

Physicians' handbook

If a separate physicians' handbook is relevant for the device, this should be provided in the languages accepted in the Member States where the device is envisaged to be sold.

Implant card information

Please provide the Implant card and information to be supplied to the patient with an implanted device, if applicable. The implant card and other information per Article 18 of MDR, and any additional information as specified in the MDCG guidance (MDCG 2019-8) on Implant cards should be included. The location of the implant card within the device or system packaging should be clearly specified. The planned approach for translation of any information not in harmonised symbols should be described if applicable.

Copies of promotional materials (that mention that the device fulfils the requirements of CE marking) including any that make specific claims related to the device

Only marketing literature that mention that the device fulfils the requirements of CE marking or includes the CE mark itself is required to be provided.

Supporting evidence should be provided in the relevant pre-clinical and clinical sections to substantiate any claims made in the labelling or marketing literature.

URL of the website where the IFU (and any other labelling information as relevant) will be made available as per GSPR 23.1

GSPR 23.1 requires that information related to identification, and safety and performance of the device shall be made available and kept up to date on the manufacturer's website if the manufacturer has a website. The URL of the website where such information will be made available should be included.

For device for which cybersecurity is applicable (MDCG 2019-16): information for healthcare providers regarding intended use environment following the requirements of MDCG 2019-16.

Design & Manufacturing Information

Please provide detailed description of manufacturing processes including:

- Manufacturing flowcharts (identifying the processes implemented and specifying whether they are validated or verified, together with the in-process and final controls performed), including where these stages are subcontracted.

- Detailed description of manufacturing procedures and controls including where these stages are subcontracted. The control criteria on the critical characteristics of the device, including where these are subcontracted, must also be provided.

- Critical process verification reports: Manufacturer should include verification protocols/plans/reports for processes that are verified (as opposed to validated) and are considered critical for the safety and performance of the device. Notified body reviewers may request this information for other verified processes (not originally included with the submission) during the review process if required.

- Incoming material testing procedures. Acceptance criteria & results of incoming inspections from a sample batch for the critical raw materials and/or sub-assemblies and/or components.

- Continuous monitoring / in-process controls. Specifications / acceptance criteria.

- Specification of final (release) product and testing. Acceptance criteria & results of final inspections from a sample batch for the finished devices.

- Identification of party responsible for inspection of subcontracted processes.

- Information on specifications and their validations (e.g. coating processes, injection moulding, bonding, welding, cleaning, rinsing, sterilisation packaging, software processes, etc.).

- Any intermediate cleaning stage(s) must be specified.

- A description of the validated manufacturing process(es) and Validation report(s) (OQ and PQ), including where these processes are subcontracted. This must at least identify the following information:

  - Description of the validated process with the precise identification of the equipment concerned.
  - Identification of associated validation reports (OQ / PQ) with their reference, revision number and revision date.
  - Identification of critical process parameters as well as validated tolerance intervals (Minimum / Maximum).

The manufacturer should include validation protocols/plans/reports for processes that are validated and are considered critical for the safety and performance of the device. Notified body reviewers may

request this information for other validated processes (not originally included with the submission) during the review process if required.

Please provide the Master Validation Plan and Validation Reports of processes considered critical for the safety and performance of the device. Please consider this requirement also for critical processes being outsourced. Further information might be requested during the Technical Documentation review and/or during audits.

Provide a description of working environment including its classification and its controls.

Provide a description of any adjuvants used.

Provide details of continuous monitoring processes.

Where a process has been the subject of a previous assessment with the same notified body in the context of Regulation (EU) 2017/745 in a Master-File format (validation of a process covering several devices covered by different Technical Documentations and / or dependent on different categories and/or generic groups), please provide:

- Identification of the process(es) concerned.
- Identification of the number and date of previous assessment report, with a satisfactory outcome.
- A rationale for the proposed inclusion of the device, which is the subject of the assessment, in the validation of the process previously assessed (inclusion of the product within a defined family without challenging the worst-case scenario).

If the device is required to be installed and/or commission at the user location, please provide information on tests to be carried out as a part of the installation and commissioning of the device.

As a general principle if any of the information requested in the Manufacturing section is not available in English, the Manufacturer should either provide translations or provide supplementary summary reports with translations of relevant information/sections or in cases where the information/reports are data heavy (or mainly graphical in nature) with very few words, the Manufacturer may annotate English translations of relevant words within the reports.

Sites and Subcontractors

The manufacturer shall provide the following documentation at a minimum:

- The name and address of any critical subcontractors or crucial suppliers (as per Commission Recommendation 2013/473/EU) should be identified, along with the service or material supplied by each.
- Copies of critical subcontractor ISO 13485 certificates or other relevant certificates based on the product / service they provide. If a critical subcontractor does not have an ISO 13485 certificate from a notified body, additional supplier audits may need to be arranged.

- Identification of subject medical device design sites (identification of all sites, including suppliers and sub-contractors, where design activities are performed, e.g. outsourced design units, research sites, etc.).
- Identification of subject medical device manufacturing process sites (identification of all sites, including information of manufacturing stages, suppliers and sub-contractors, where manufacturing activities are performed).
- Quality assurance agreements with subcontractors (in case of sterile medical devices, the contract with the sterilisation company).
- Suppliers and subcontractors (name and address of the company, evidence of qualification of subcontractors, e.g. certificates, accreditation certificate, etc.).
- If multisite companies are present, specify the site(s) involved in the design / manufacturing of the subject medical device.

General Safety & Performance Requirements (GSPRs)

The manufacturer should provide documentation in the form of checklist that includes the following:

(1) - Each GSPR of MDR Annex I that applies to the device and an explanation as to why other GSPRs do not apply to the device.

- EXAMPLE: A decision column "applicable versus not applicable" for each clause/sub-clause of MDR, Annex I. A "rationale" column on each clause/sub-clause of MDR, Annex I, that apply to the device, with an explanation as to why others do not apply.

(2) - The method or methods used to demonstrate conformity with each applicable GSPR.

- EXAMPLE: A column "methods used to demonstrate conformity", with each clause/sub-clause of MDR Annex I

(3) - Harmonised standards, Common Specification (CS), or other solutions applied (please refer to the specific edition).

- EXAMPLE: A column "applied standards, CS or others", for each clause/sub-clause of MDR, respectively.

- NOTE 1 to (3): This is usually accomplished by means of a list of applicable standards and CS, as well as by reference to appropriate standards and CS in the appropriate documents (e.g. test reports).

- NOTE 2 to (3): Indicate if full or partial compliance is being claimed. Where (i) key standards or CS have not been applied or not been applied in full, (ii) a manufacturer chooses to use a newer version of a currently harmonised standard, (iii) outdated standards are applied: in all these cases, an appropriate justification should be provided in the Technical Documentation, in the form of a summary or gap analysis regarding ability to comply with associated General Safety & Performance Requirements (Annex I), and a risk analysis & conclusion of acceptability of any compliance gaps.

- NOTE 3 to (3): Refer also to additional applicable standards, and/or Directives – e.g. Machinery, EMC, RoHS, scientific opinions, guidance as necessary to show state of the art.

(4) - 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 GSPR.

- EXAMPLE: A column to add the "precise identity of the controlled documents" offering evidence of conformity.

- NOTE 1 TO (4): This shall include a cross- reference to the location of that document within the full Technical Documentation (identification should be as "Document ID, section, point, page") and, where applicable, the summary of the technical documentation. The more specific the references are to documents supporting compliance, the faster the review can be conducted.

- NOTE 2 to (4): If no new testing is deemed required, a justification needs to be provided.

(5) - Approval by the responsible person (date, signature).

Benefit Risk Analysis and Risk Management

For risk management please refer to the MDR requirements as stated in Annex I, clauses 1-9 and Annex II, section 5. Please clearly indicate whether the risk management process is based on EN ISO 14971.

The interface between risk management process and data from pre-clinical evaluations (product verification and validation) and clinical evaluation performed by the manufacturer must be clear and noticeable (refer to Annex VII, 4.5.4(c) and 4.5.5.); and the results of the risk management shall provide information about the appropriateness of the pre-clinical and clinical evaluation.

Please provide a copy of risk management procedure(s) that include the definition of any rating systems used for risk analysis and risk acceptability. If this is part of a different document such as the risk management plan or maintained as a separate document that is specific for the subject device, then the relevant information must be included.

Please provide copies of the relevant risk management documentation to confirm that the risk management procedure is followed (including e.g., the usability risk management procedure, if applicable). Evidence of the "life-cycle management" concept must be provided, i.e., the analysis must be performed throughout the life cycle of the device, from design to disposal, considering all the appropriate PMS data.

Please note that risk management documentation shall comprise all parts / components of a device. Risk management shall be understood as a continuous iterative process throughout the entire lifecycle of a device, requiring regular systematic updating.

The requirements also apply in case of outsourced processes.

Risk management plan

Please provide the risk management plan associated with the device, including:

- The scope of the risk management activities.
- The complete description and identification of the devices and accessories in question.
- The description of the life cycle phases of the device.
- Assignment of responsibilities and authorities for risk management.
- Identification of requirements for review of risk management activities.
- The system used for qualitative or quantitative categorisation of – as a minimum - probability of occurrence of harm and severity of harm.
- Definition of criteria for acceptable risk levels.
- Evaluation of any residual risk acceptability, including overall residual risk.
- Criteria for acceptability of the overall residual risk, the method and evaluation of overall residual risk.
- Verification of the implementation of risk control measures.
- Verification of the effectiveness of risk control measures.
- Identification of activities for collection and review of production and post-production information.

Please provide the qualification (resumes) of the risk assessment team and explain why the manufacturer deems its competence as being appropriate (including assignment and qualification of clinical expert).

Risk analysis / risk control measures

The documentation shall contain information on:

- The benefit-risk analysis referred to in section 1 and 8 of MDR Annex I.
- The solutions adopted and the results of the risk management referred to in section 3 of MDR Annex I.
- Evidence given that a safety concept in accordance with section 4 of MDR Annex I is applied, including information to users of any residual risk(s).

The documentation shall include:

- Design risk assessment: documented risk assessment for the design aspects of the device.
- Production/process risk assessment: documented risk assessment for the production / manufacturing process aspects of the device.
- Clinical/Application/Product risk assessment: documented risk assessment for the clinical usage / application aspects of the device.
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For design risk assessment, an assessment shall be provided whether any design changes add new hazards or reduce the likelihood of occurrence of existing hazards, irrespective of whether the risk assessment has changed.

Reduction of the risks related to use error shall cover the requirements set out in section 5 of MDR Annex I. For usability evaluation please refer to the MDR requirements stated in Annex I, clauses 14.6, 21.3, 22.1, 22.2, 23.1a, as well as to EN 62366-1.

For ease of review, it is recommended to provide a use flow-chart for the device in question.

Risk analysis shall demonstrate:

- All known and foreseeable hazards associated with each device are identified and analysed (i.e., estimation and evaluation of risks for each hazardous situation).
- All known and foreseeable risks, and any undesirable side-effects, are minimised and acceptable when weighed against the evaluated benefits to the patient and/or user arising from the achieved performance of the device during normal conditions of use.
- Estimation and evaluation of risks associated with and occurring during intended use and during reasonably foreseeable misuse are estimated and evaluated, including eliminating or controlling these risks.
- Appropriate controls (i.e., process validations, biocompatibility, sterilisation, clinical, shelf-life or other key verification/validation tests) have reduced all risks as low as possible to acceptable levels considering state-of-the-art for the product(s) under assessment.
- Risk control measures are implemented for each hazard (with references to the documentation where these measures are implemented).
- The effectiveness of risk control measures is verified (with references to the documentation where effectiveness of risk control measures is demonstrated).
- Residual risks and their processing operations are identified, and the acceptability of any residual risk(s) is assessed.
- A statement is given that the medical benefits outweigh all the residual risks.
- Production and post-production information are evaluated regarding hazards and their associated risks, as well as on the overall risk, benefit-risk ratio and risk acceptability; and the control measures are amended if necessary.

The risk analysis shall cover (not limited to):

- Hazards related to all device components.
- Hazards related to clinical use.
- Hazards related to ergonomic features of the device and the environment in which the device is intended to be used.
- Hazards related to technical knowledge, experience, education, training and use environment of users.
- Hazards related to the medical and physical conditions of intended users (lay, professional, disabled, etc.).
- Hazards related to reuse (please note for single-use devices, GSPR 23.4(p) requires the risks of re-use to be addressed, this should be identifiable).
- Hazards related to the manufacturing process.
- Hazards related to cybersecurity.
-

Note: additional hazards are also given in EN ISO 14971.

<u>Risk management report</u>

Please provide the risk management report associated with the device, including:

- The evaluation of any residual risk(s) acceptability.
- The evaluation of the overall residual risk acceptability.
- The evaluation of the benefit-risk ratio.

A statement shall be provided that the device, when used within the intended purpose, constitutes acceptable risks when weighed against the benefits to the patient and is compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art (MDR, Annex I, 1).

For MDR Annex XVI devices: a statement shall be provided that the device does not present a risk at all or presents a risk that is no more than the maximum acceptable risk related to the device use, which is consistent with a high level of protection for the safety and health of persons (MDR, Annex I, 9).

Product Verification and Validation

Biocompatibility

The following information is to be provided for biocompatibility product verification and validation:

1. Standards and references applied for the medical device related to biological evaluation.

• Standards and references applied in terms of biological evaluation. When specific standards exist for the type of medical devices, it is recommended to use the most specific standard, or the one with the highest level of requirement.

• If applicable, justification of the equivalence between the used reference and the applicable standard.

2. Formulation, description, manufacturing and use of the medical device.

• Description of medical device formulation.

• Description of the expected and intended biological effect, if applicable.

• Verify the consistency between the following information, contained in the biological evaluation presented and the technical documentation:

- Manufacturing of the medical device: methods, adjuvants/additives (aids).

- Use of the medical device in the target population, including the claimed clinical performance, lifetime, shelf-life and storage conditions.

3. Categorisation of the medical device: nature and duration of contact.

• Nature of the contact with the human body.

• Duration of the contact with the human body.

4. Identification of potential biological risks of the medical device / possible biological hazards.

• Parameters associated with the nature and contact of the device which are to be evaluated under the assessment of the biological risk.

5. Physical and chemical information for biological risk analysis / medical device characterisation.

• Material characterisation protocol.

• Identification, selection, collection and review protocol of all existing data and studies.

• Thorough characterisation of the materials according to ISO 10993-1 including the potential device leachables, based on the literature review of the toxicological data available on components / adjuvants (cf. ISO 10993-17 for the toxicological acceptance levels).

• Copies of test reports performed according to ISO 10993-18, if applicable.

• Justification of the selection of the test article (as being representative of the device) and relevance of the tests performed.

• Evidence of the ISO 17025 accreditation or equivalence of the testing laboratory.

• Results of the tests performed.

• Description of the methodology for calculating the safety margins (analysis according to ISO 10993-17, if applicable).

• Where the potential of degradation exists, determine the presence and the nature of degradation products. Their characterisation must be performed according to ISO 10993-9, and then 10993-13, 10993-14 and 10993-15, depending on the material considered, at different stages of the lifecycle of the device if relevant.

• Presence of a report dated and signed by the competent reviewers, along with the articles used and data relating to the substances.

6. Biological testing program.

• Justification on the need or not to perform biological evaluation tests to respond to the risks previously identified (section 4) which cannot be controlled by the bibliographic data.

• Determination of the testing program.

• For each test defined in the testing program, the following information must be documented in a report:

- Description of the test method used.

- Standard applied.

- Competence of the testing laboratory.

- Justification of the test article selection as being representative of the medical device.

- Test conditions.

- Results obtained.

• Relevance of the tests performed.

• Reports of the tests performed.

• Evidence of the ISO 17025 accreditation or equivalence of the testing laboratory.

7. Overall analysis of the results.

• Overall evaluation to demonstrate the control of all potential risks at an acceptable level and the benefit to health from the use of the device as intended by the manufacturer, against probable risks of injury or illness from such use.

• Reference to the risk management file, allowing the tracking of the analysis and the control of the biological hazards.

• Reference to the data collected as part of the Post-Market Surveillance (PMS) allowing the verification of their consideration in the biological risk assessment report.

Software & Software Validation (Including Cyber Security)

General Overview

A clear statement and documented rationale as to why the product is a Software as a Medical Device (SaMD) is required.

Based on the standard used for compliance, a standards compliance checklist to the requirements based on the software's risk category is recommended. Direct references to where in the technical file the evidence of meeting the requirements of the chosen standard is located should be present in any compliance checklist presented.

If a different standard has been used than that of the harmonised version(s), then a detailed document shall be provided that explains how the requirements of the harmonised version have been met or exceeded shall be provided along with the evidence.

The Software safety classification shall be provided and the justification for it shall be clearly identified in the technical file. The software version under application shall be clearly identified in the application.

Traceability matrices that contain traceable sources to requirements (risk, regulatory performance etc.) and in turn the identification of the protocols reports and test data documents relating to their verification and validation test evidence are beneficial to the review. As stated previously, these documents should also be submitted in the technical documentation.

The software standards applied to the device should also be identified in the technical documentation, provide evidence of consideration of all related harmonised and non-harmonised /STOA software standards / guidance(s).

Note: Some documentation may or may not be required per the standards based on software system/module/item risk classification.

Software

Common required documentation

Across the notified bodies selected, the following common documented evidence is required at a minimum in the technical document. Please note that this list is dependent on the software risk classification of the device under application. All required activities of the chosen standard for compliance shall be demonstrated in the file.

Software development plan

The software development plan shall be included and relevant procedures/ description which communicate the software development process and the lifecycle requirements. This shall be in conjunction with the system development plan if applicable.

Class B and C should include documentation describing the development environment used (tools, elements, settings, etc.).

Software requirements analysis

The software requirements analysis should be provided - this should include but is not limited to:

- Functional and non-functional (timing, stress language scalability, etc.) requirements.
- Requirements derived from potential software defects and information derived from previous designs.
- Requirements relating to the use of the device e.g. installation.

- Evidence that the requirements analysis considered MDR Annex II 17.4, especially hardware requirements, IT network characteristics (if applicable), and security requirements in relation to access control and unauthorised access.
- Evidence in the documentation information relating to the functionalities, capabilities, input data, output data, system interfaces, alarms, security requirements, cybersecurity requirements, user interface requirements, database requirements, installation requirements, requirements related to methods of operation and maintenance, regulatory requirements, etc.

Software architectural design

The architecture design should be provided, it is acknowledged that it can have graphical representations (UML, class diagrams, blocks etc.) but it should demonstrate how the requirements are allocated to software items that make up the overall software system. The architectural design should consider the internal and external interfaces of the software, the functional and performance requirement of SOUP and its additional hardware and software requirements. Depending on the risk class, it may be required to include segregation measures for risk control purposes, these should also be included here.

Software detailed design

For Class B & C risk-based devices, a further refinement of the software architecture is required. A clear identification of the software units that are derived from software items should be provided. This should contain the design data for each software unit and any interfaces between the units and any external components. Details should be provided on the expected inputs and outputs for each software unit.

Verification and Validation

All plans, protocols, reports and test data relating to verification and validation testing performed in-house and or in simulated use or actual use environment must be submitted.

Documentation detailing the test environment should also be included in the application.

Clearly identify where automated testing has been used in verification activities and include the test scripts and test log results in an organised manner in the documentation.

System level test plans/protocols and repots shall be provided.

Evidence that the different hardware and, where applicable, the different operating systems have been verified/validated should be clearly identified and supplied by the manufacturer.

If the software is for use with mobile platforms, information demonstrating compliance with GSPR 17.3 should be provided.

The standards used for the validation of standalone software should be clearly presented and the required validation documentation provided.

Traceability matrices(s) between software testing and specifications (system specifications/system verification, unit specifications/unit verification, etc.) should be provided.

Evidence of the verification of SOUP items shall be included.

In addition to the individual reports, it can also be beneficial to submit an overall Verification and Validation summary report that identifies the following:

- The software version.
- A summary of test results.
- Details on any errata or unresolved anomalies, including evidence and a risk rationale as to why these are acceptable.
- Conclusion on acceptability.
- Details on the roles and functions approving the summary.

Software release

Include the list of known residual anomalies. The following information on each remaining anomaly should be included:

• Unique Identifier.

• Brief description of the issue.

• Severity/Risk Level.

• Justification for why it is acceptable to release the software with the anomaly.

Evidence in the technical file shall also include evidence demonstrating how the released software was created (e.g., procedure and environment used to create the released software). The final released software version number should be clearly identified in this documentation.

Evidence explaining how the released software is archived and how it can be reliably delivered (e.g. to the manufacturing environment or to the user of the software) should be included. Evidence that all required tasks prior to release were completed should be included in the release notes.

Software risk assessment

The manufacturer should include all software risk assessment documentation (e.g., software hazard analysis, software failure mode and effects analysis, fault tree analysis, traceability etc.).

Note: Some documentation may or may not be required per the standards, based on the software system/module/item risk classification.

Cyber security

The documentation in relation to the secure design and ongoing maintenance of the medical device in respect to cyber security should be submitted. The manufacturer shall clearly state the harmonised or SOTA standard(s) of compliance used for conformance to the relevant GSPRs.

The manufacturer shall provide evidence of a security risk management system that supports a secure development lifecycle, some examples include:

Security risk management plan, security risk assessment and evidence of the incorporation of security risk controls as identified requirements and evidence of their subsequent verification and validation.

The identified threats protections incorporated shall align with the principles of Confidentiality, Integrity, and Availability (reference MDCG 2019-16 Guidance on Cybersecurity for medical devices).

The manufacturer should provide the technical documentation that clearly identifies the method for identifying the ongoing monitoring of threats and vulnerabilities as well as the methodologies used e.g., STRIDE, attack surface analysis, data flows etc. Documentation shall show how cybersecurity is an active part of ongoing post market surveillance of the device.

The manufacturer shall provide documented evidence for the monitoring of ongoing risks associated with SOUP vulnerabilities and their mitigation.

Where necessary, evidence of certified/accredited penetration testing should be provided including certification details of the third party and test reports.

Where cloud-based software providers are utilised, there should be evidence in the technical file of the assigned responsible parties for post market surveillance and the reporting of security issues.

Electrical Safety and Electromagnetic Compatibility (EMC)

This chapter is only relevant for electrical medical device(s).

The manufacturer should provide the following documentation:

Electrical safety test protocols & Electrical safety test reports.

- Please provide the test protocols and reports for electrical safety testing.

EMC test protocols & EMC test reports.

- Please provide the test protocols and reports for EMC testing. Test protocols may be embedded as part of the test report.

Please include:

- Overview of tests performed.
- For tests conducted by a test laboratory include the test reports, certificate and evidence of accreditation of the test laboratory.
- For safety testing, please provide a description of requirements related to the periodic tests and tests after repairs (e.g. EN 62353).
- For in-house testing, evidence of the competency of the personnel involved is required as well as evidence of calibration of test equipment/facilities and QMS procedures.
- MRI safety testing of the device/system (MDR Annex II Section 6.1(b)) shall be included if relevant.
- In cases where an assessment refers to an evaluation report or any company document more than 5 years old, the corresponding data must be provided and a rationale explaining why it remains applicable shall be included.

Notes:

- Ensure the provided documentation clearly defines the ESSENTIAL PERFORMANCE of the device and is in line with the risk management documentation (including analysis, plan and reports). Test reports shall include evaluation of data and conclusions.
- If a subset of devices has been selected for testing and this subset is intended to represent a larger range of devices, provide supporting documentation that demonstrates how the configurations that have been tested can be considered representative of the wider set of devices/configurations.
- Relevant standards are the EN 60601 series, including EN 60601-1-2 for EMC and EN 60601-1-6 and/or EN 62366 for usability as well as standards in the 80601 series (essential performance).
- When the device is designed to be used sterile, testing should be performed on the sterile device.
- The safety of devices emitting ionising radiation and electrical devices in relation to these characteristics must be considered.

Packaging, Stability and Shelf-Life

The following information should be provided:

- Description of packaging types used - primary, secondary etc.
- Claimed shelf life and evidence, i.e. written evidence and justification with example of the label.
- Assessment of changes within packaging.
- Storage conditions.
- The standards used for testing.
- If packaging/stability/shelf-life is being leveraged from another product, a detailed rationale should be provided on why this is appropriate.

For sterile packaging:

- Certificates/COA - for the packaging materials used to ensure the packaging is suitable for the sterilisation method used.
- Accreditation certificates for the testing facility.
- Real time aging should be performed in parallel to the accelerated aging. If the real time aging test reports are not available, then the plan should be presented covering when the real time test will be completed.
- Protocol for the shelf-life studies covering product functionality as well as packaging integrity – accelerated aging and real time aging to be provided.
- Reports for the shelf-life studies covering product functionality as well as packaging integrity – accelerated aging and real time aging to be provided.

For Nonsterile packaging – if the shelf life is claimed:

- Certificates/COA - for the packaging materials used.
- Accreditation certificates for the testing facility.
- Protocol for the shelf-life studies covering product functionality – accelerated aging and real time aging to be provided.
- Reports for the shelf-life studies covering product functionality – accelerated aging and real time aging to be provided.

Transportation (transit) testing:

- Protocol/test report for transit testing covering the standard storage and shipping conditions, product functionality and packaging test post-transit testing etc.

Performance and Safety - Design Verification and Validations (including devices with a measuring or diagnostic function, MR Compatibility)

The manufacturer should provide the following documentation:

Overview of all testing performed.

Protocol and reports with evidence of compliance with design requirements including measurement accuracy and range, output generated, stability, functions, features, dimensions, accuracies etc.

Testing to relevant standards (e.g. EN 80601 series [essential performance] for Active medical devices) shall be provided if compliance to these is claimed. Protocol & report shall provide the evidence for all variants/configurations of the device, shall cover interconnections to accessories and parts of the device.

Evidence shall demonstrate compliance for the environmental conditions specified for the device and for the lifetime of the device (or service periods prescribed).

If the device is to be connected to other device(s) to operate as intended, a description of this combination/configuration including proof that it conforms to the general safety and performance requirements when connected to any such device(s) having regard to the characteristics specified by the manufacturer.

For tests conducted by a test laboratory, include the test reports, certificate and evidence of accreditation of the test laboratory

For in-house testing, evidence of the competency of the personnel involved is required as well as evidence of calibration of test equipment/facilities and QMS procedures.

MRI safety test protocols and reports, together with labelling relevant for MRI Safety, as relevant for the device.

Usability

Please provide the protocols, data and results for usability studies.

The following is expected when compliance to the relevant European standards (EN62366 and EN60601-1-6) is claimed: Usability engineering file, including the following information: Use specification, Identification of user interface characteristics related to safety and potential use errors, Identification of known and foreseeable hazards and hazardous situations, Identification and description of hazard-related use scenarios, Selection of the hazard-related use scenarios for summative evaluation, User interface specification, User interface evaluation plan, User interface design and implementation, Formative evaluation and Summative evaluation.

The usability documentation shall be in line with the risk management process.

Specific for devices intended for use by lay persons: verification the device performs appropriately for the intended purpose considering the skills and the means available to lay persons and the influence resulting from variations that can be anticipated in the layperson's technique and environment.

Accompanying documents include a concise description of the medical device, which includes the operating principle, signification physical characteristics, significant performance characteristics and the intended user profile.

Specific for devices intended for use by lay persons: the information and instructions are considered easy to understand and apply.

Devices Incorporating Medicinal and Biological Materials

Drug/Device Combination Products

Devices incorporating as an integral part a substance, which if used separately, may be considered a medicinal product in the meaning of Directive 2001/83 EEC.

The submission should clearly indicate whether the device utilises, or is used in conjunction with, any medicinal substances. If the device is a system and includes multiple components, then identify the components which incorporate these medicinal substances.

Devices which incorporate medicinal substances may be subject to requirements of additional European Directives / Regulations. Additional review resources may be required, including external independent reviewers and/or Competent Authority consultation and/or a European Agency for the Evaluation of Medicinal Products (EMA).

Please provide the following data:

- Applicability of device including a medicinal substance(s).

Recommendation:

Explanation for classification of the product as device incorporating as an integral part an ancillary medicinal substance.

- Intended purpose of the product.

- Type of product, brief description and method by which the principal intended action is achieved.

- Mechanism of action. Ancillary action to the device.

- Indications, application of the device.

- Justification for the use of medicinal substance(s).

Recommendation:

Background related to substance:

- How it is incorporated.

- The purpose for the incorporation of the medicinal substance

- Information and identification of medicinal substance(s).

Recommendation:

Presentation of the substance (quantitative and qualitative composition).

- Regulatory status of similar products. Related risk assessment (either stand-alone or as a part of the risk management section) for use of medicinal product.

Recommendation:

Critical appraisal of the results of the risk assessment (either stand-alone or as a part of the risk management section for use of medicinal product). Please note that these documents shall also be part of the Common Technical Document (CTD).

- Description of production, processing, preservation, testing and handling of medicinal product.

- Summary and test protocols/reports on the safety, quality and usefulness of the medicinal product taking account of the intended purpose of the device.

- Validation method and reports in the manufacturing process.

- Preclinical and biocompatibility data.

- Stability tests.

Clinical Data (CER)

- Clinical Evaluation of Literature data, including references.

- Clinical pharmacokinetic testing.

- Additional clinical investigation confirming the safety and usefulness (in accordance with EN ISO 14155).

- Usefulness: Evaluation of the usefulness in relation to the safety of the medicinal substance as part of the medical device considering the intended purpose of the device.

Recommendation:

The usefulness of the ancillary medicinal substance incorporated in the medical device should be addressed by clinical evaluation or by cross-reference to other sections of the dossier, as applicable.

For the Medicinal substance:

Recommendation

CTD including Modules 1-5.

To perform their assessment, the Competent Authorities (CA) prefer the documentation to follow the CTD structure [i.e., Non-eCTD electronic Submission (NeeS)]. Presentation of the data in line with CTD principles will facilitate an efficient review by the selected CA. A NeeS guidance document can be found on the eSubmission website. A CTD folder structure template is available for download on the ICH web site (note that this template lacks Module 1, which you will have to create yourself, preferably in line with the "File-Folder Structure & Names" tab in the NeeS Validation Criteria document). All study reports/literature references (full text) should be included in the documentation.

The available applicable guidance on the content of the CTD shall be taken into consideration when collating the dossier. Also note that different Competent Authorities may have slightly different requirements and the specific advice may be available on their websites and should be taken into consideration.

Human Origin Matter

Devices utilising tissue and cells of human origin or their derivatives according to MDR Annex I, GSPR 13.2.

The submission should clearly indicate whether the device utilises or contains any human-based products. If the device is a system and includes multiple components, then identify the components which incorporate these substances.

Manufacturing subcontractors should be consulted, if appropriate, to establish if any such substances are used during manufacture, even if they do not feature in the final device.

Devices which incorporate human-derived substances may be subject to requirements of additional European Directives / Regulations. Additional review resources may be required, including external independent reviewers and/or Competent Authority consultation and/or a European Agency for the Evaluation of Medicinal Products (EMA).

Please provide the following data:

- Applicability of human origin material.

- Justification for the use of human tissue material.

- Identification of human origin material and/or composition for all components including coatings and surface treatments.

- Quantity of material in one device, number of treatments possible, route of administration.

- Explanation / justification of use of human origin material in comparison with alternative products.

- Information on the nature of the human starting tissue.

- Human origin material related risk assessment (either stand-alone or as a part of the risk management section).

- Description of sourcing, processing, preservation, testing and handling of human origin materials or their derivatives.

- Summary and test protocols/reports on the safety, quality and usefulness of the human tissues and cells or their derivatives, considering the intended purpose of the device.

- Validation method and reports of elimination or viral inactivation in the manufacturing process including possible inactivation / elimination processes regarding prions, as CJD and other TSEs are applicable for human tissues in general.

- Copy of labels and IFU submitted in Section 2, including relevant information related to the human tissues or cells or derivatives utilised or contained in the device as per GSPR 23.2 and GSPR 23.4(s).

Animal Origin Matter

Devices utilising tissue and cells of animal origin or their derivatives according to MDR Annex I, GSPR 13.2.

The submission should clearly indicate whether the device utilises or contains any animal-based products. If the device is a system and includes multiple components, then identify the components which incorporate these substances.

Manufacturing subcontractors should be consulted, if appropriate, to establish if any such substances are used during manufacture, even if they do not feature in the final device. The manufacturer should request evidence of compliance to ISO 22442 or EU 722/2012 or for any applicable exclusions (e.g., tallow species and processing method utilised) from the subcontractor.

Devices which incorporate human or animal-derived substances may be subject to requirements of additional European Directives / Regulations. Additional review resources may be required, including external independent reviewers and/or Competent Authority consultation and/or a European Agency for the Evaluation of Medicinal Products (EMA).

Please provide the following data:

- Applicability of animal origin material.

- Justification for the use animal tissue material.

- Identification of animal origin material, including TSE risk category according to WHO definition.

- Quantity of material in one device, number of treatments possible, route of administration.

- An estimate of the TSE risk arising from the use of the product, considering the likelihood of contamination of the product, the nature and duration of patient exposure.

- TSE certificate of suitability issued by EDQM.

- Explanation/ justification of use of animal origin material in comparison with alternative products.

- Information on the nature of the animal starting tissue, animal species and geographical nature.

- Animal origin material related risk assessment (either stand-alone or as a part of the risk management section).

- Evidence on compliance with EN ISO 22442-1, -2 and -3.

- Description of sourcing, veterinary controls, geographical origin of the animals, stunning/ slaughtering, processing, preservation, testing and handling of tissues, cells and substances of animal origin or their derivatives.

- Summary and test protocols/reports on the safety, quality and usefulness of the tissues and cells, considering the intended purpose of the device.

- Validation method and reports of elimination or viral inactivation in the manufacturing process. TSE inactivation / elimination is applicable for the processes. At the very least, a respective literature review for the entire processes shall be applied, see EU 722/2012. An exceptional case is if the device does not withstand rigorous inactivation / elimination processes.

- Description of the avoidance of cross contamination during manufacturing steps up to the final packaged device and the measures taken; the amount of pooling, e.g., for biological heart valves, shall be defined in case of TSE relevant material.

- Evidence on compliance with EU 722/2012 in case TSE relevant material is used.

- Copy of labels and IFU submitted in Section 2 including relevant information related to the animal tissues or cells or derivatives utilised or contained in the device as per GSPR 23.2 and GSPR 23.4(s).

Biological Origin Matter

For devices manufactured utilising other non-viable biological substances please provide the following data:

- Applicability of utilising other non-viable biological substances.

- Identification of non-viable biological substances utilised.

- Methods for identification of microbial production strain and for strain maintenance in master cell bank, working cell bank and production cell bank shall be defined.

- Description of preservation, testing and handling of those substances, sourcing, waste disposal chain, considering the composition of the master call bank, working cell bank, fermentation and media thereof.

- Justification that the materials used are safe for their intended use, for patients, users, and where applicable, other persons.

- Safety regarding viruses and other transmissible agents using appropriate methods of sourcing.

- Validation report for elimination or inactivation during the manufacturing process.

- Consideration of fermentation / production residuals in the purified bulk substance, consideration of cell debris and residuals (DNA, RNA residuals) in the final purified bulk substance, including exotoxins released by bacterial strain.

- Risk analysis of the manufacturer concerning use of the biological origin material and the risks stated above.

Substances absorbed or locally dispersed

Devices composed of substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body to achieve their intended purpose (Rule 21, MDR Annex VIII).

MDR Annex I, GSPR 12.2 requires for devices that are composed of such substances to consider the relevant requirements of Directive 2001/83/EC in relation to absorption, distribution, metabolism, excretion (commonly referred to as ADME profile), local tolerance, toxicity, interaction with other devices, medicinal products or other substances and potential for adverse reactions.

Devices that are composed of such substances may be subject to requirements of additional European Directives / Regulations. Additional review resources may be required, including external independent reviewers and/or Competent Authority consultation and/or a European Agency for the Evaluation of Medicinal Products (EMA).

Please provide the following data:

- Applicability of such substances that are systemically absorbed or locally dispersed.

- Identification of such substances that are systemically absorbed by or locally dispersed in the human body.

- Address the specific aspects related to absorption, distribution, metabolism and excretion tests, toxicity (ADMET).

- In general, for devices consisting of substances in relation to Rule 21, tests for product characterisation, for proper qualification as a medical device (mechanism of action) and for establishing the right classification according to Rule 21 are deemed necessary.

- Information and/or test data related to these requirements should be included in the Technical Documentation. If evidence is based on published literature, manufacturers should rationalise the applicability of such literature data to their own device considering the nature of their device, intended purpose, contact with various body tissues and other substances, the target population, and its associated medical conditions etc.

- Test protocols and reports for determining the absorption, distribution, metabolism, excretion of those substances.

- Test protocols and reports for determining the local tolerance of those substances (refer to biocompatibility).

- Test protocols and reports for determining the possible interactions of those substances, or of their products of metabolism in the human body, with other devices, medicinal products, or other substances.

- Test protocols and reports for determining the toxicity of those substances including single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, as applicable depending on the level and nature of exposure to the device (refer to biocompatibility).

- Justification in case above mentioned studies on absorbable or locally dispersed materials are not performed/provided. Please add a scientific based justification in case related tests on absorbable or locally dispersed materials are not performed/provided.

Hazardous substances, CMR, endocrine disrupting substances

Devices containing CMR or endocrine-disrupting substances referred to in GSPR 10.4.1 of Annex I of MDR: GSPRs 10.4.1 - 10.4.5 describe specific requirements for devices that contain substances which are carcinogenic, mutagenic or toxic to reproduction and substances having endocrine-disrupting properties.

Information and/or test data related to these requirements should be included in the Technical Documentation. This information may be provided either as a stand-alone section or incorporated into other relevant sections such as biocompatibility, labelling etc.

Please provide the following data:

- Applicability of CMR substances (carcinogenic, mutagenic or toxic to reproduction) substances having endocrine disrupting properties in a concentration of > 0.1% w/w acc. to GSPR 10.4.1.

- List substances in a concentration of > 0.1% w/w.

- If evidence is based on published literature, manufacturers should rationalise the applicability of such literature data to their own device considering the nature of their device, intended purpose, contact with various body tissues and other substances etc. Or, planning and overview as well as reports of tests performed, evaluation of data and test results.

- Justification according to GSPR 10.4.2 for use of substances in a concentration of > 0.1% w/w including:

  - An analysis and estimation of potential patient or user exposure to the substance.
  - An analysis of possible alternative substances, materials or designs, including, when available, information about independent research, peer reviewed studies, scientific opinions from relevant Scientific Committees and an analysis of the availability of such alternatives.
  - Argumentation because possible substance and/ or material substitutes or design changes, if available, are inappropriate to maintain the functionality, performance and the benefit-risk ratios of the product; including considering if the intended use of such devices includes treatment of children or treatment of pregnant or nursing women or treatment of other patient groups considered particularly vulnerable to such substances and / or materials.
  - Where applicable and available, the latest relevant Scientific Committee guidelines (as per GSPR 10.4.3 and 10.4.4).

- Copy of labelling including the list of such substances in a concentration of > 0.1% w/w on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging.

- Copy of IFU: If the intended use of such devices includes treatment of children or treatment of pregnant or breastfeeding women or treatment of other patient groups considered particularly vulnerable to such substances and/or materials, information on residual risks for those patient groups and, if applicable, on appropriate precautionary measures is given in the instructions for use.

Note: a process to identify and regularly update CMR or endocrine disrupting substances using relevant standards: CLP regulation + ATPs (Adaption to Technical Progress), ECHA webpage, REACH, SVCH list, Commission Delegated Regulation (EU) 2017/2100, SCHEER guideline refers to ECHA's endocrine disruptor (ED) assessment list and ECHA list for Biocidal Products Committee opinions on active substances will be part of an audit.

Sterilisation & Reusable Surgical Instruments

Sterilisation

Product supplied Sterile - Sterilisation

1- Confirm the types of standard and claimed SAL used for the selected sterilisation method i.e.
   - ETO-EN ISO 11135.
   - Irradiation by Gamma/E beam -EN ISO 11137-1, EN ISO 11137-2, ISO 13004.
   - Steam- EN ISO 17665-1.
   - Aseptic processing – ISO 13408 series.
   - Others.

2- Name and address of the sterilisation facility and relevant documentation – if outsourced:

- Technical agreement with sub-contractors – device manufacturer and sterilisation company.
- QMS ISO certificate confirming the sterilisation facility complies to perform sterilisation for relevant standard.

3- If performed in-house – IQ, OQ, PQ data.

4- Sterilisation parameters.

5- Example of IFU and Label.

6- Sterilisation validation and revalidation:
   - Procedure confirming the sterilisation controls i.e. validation, revalidation, routine release and frequency as per relevant sterilisation standard used.
   - Procedure confirming bioburden test controls, endotoxin test controls, clean environment test controls and frequency.
   - Product family assessment and selection of the product for sterilisation validation i.e. PCD.
   - Protocol and report for the original sterilisation validation - covering all data.
   - Protocol and report for the most recent sterilisation re-validation sterilisation validation - covering all data.
   - Sterility testing - validation of test method as per ISO 11737-2 and results.
   - Bioburden testing - validation of test method as per ISO11737-1 and -2 most recent bioburden results.
   - Endotoxin test validation and two most recent results.
   - Environmental monitoring and validation of the controlled environment - clean room microbial monitoring and physical clean room validation - most recent results.
   - Annual sterilisation assessment to confirm changes within the sterilisation process, manufacturing process, packaging changes etc.

- Additional information based on the sterilisation method used:

Ethylene Oxide documents to include:

- PCD, IPCD, EPCD information, EO residuals report, information on EO gas specification and certificate, biological indicators and certificate.

Radiation documents to include:

- Calibration details/certificates of the dosimeters used.
- Dose setting/dose substantiation Method 1, VDmax. Method 2 original validation report and if conducted for a product family, rationale for the device being in the family.
- Dose audit data trend and two most recent dose audit reports, if frequency in dose audits reduced then a justification for reduction.
- Dose mapping for min-max dose range.

Steam – PCD, Biological indicators and certificate.

Aseptic – Justification for use of this method, Process simulation Original Validation reports, Media fills Initial PQ, Media fill Periodic Performance Requalification PRQ reports, as per applicable standards, Media Selection & Growth Support, certificate for the filter used and Validation of Fluid-Specific Microbial Retention by Filters.

Product Supplied nonsterile and to be sterilised by end user:

- Example of IFU and Label.
- Sterilisation parameters.
- Validation against the IFU claims i.e. Washing, cleaning, repackaging, sterilisation, reprocessed based on the max number of usages.
- Assessment of changes.
- Bioburden data.
- Residual tests if applicable for the disinfectants used.

Reusability/ Reprocessing - Class Ir - Reusable surgical instruments:

- Name and description of the device.
- UDI.
- Intended use and classification.
- Declaration of conformity.
- GSPRs.
- Labelling and IFU.
- Applicable standards.

- Design, manufacturing and bench testing.
- Product functionality test covering maximum number of reuses as per IFU.
- If applicable - packaging, shelf-life and lifetime validations as per packaging shelf-life sections depends on product sold sterile or non-sterile or to be sterilised by end user.
- Disinfectant, cleaning, sterilisation - Protocol and reports for validations as per parameters listed within IFU.
- Reusable aspects only for below:
  - Risk assessment.
  - PMS.
  - Vigilance reports.
  - Complaints.
  - Biological safety.
  - Clinical evaluation.

Clinical Evaluation (Includes SSCP labelling)

In line with MDR Article 61 (1): *Confirmation of conformity with relevant general safety and performance requirements set out in Annex I under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit-risk-ratio referred to in Sections 1 and 8 of Annex I, shall be based on clinical data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III.*

The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose.

To that end, manufacturers shall plan, conduct and document a clinical evaluation in accordance with this Article and Part A of Annex XIV.

The following documents should be provided for the clinical evaluation assessment and when not provided a suitable justification should be provided for their absence.

(a) Clinical development strategy of the device.

- Where an opinion has been provided by the expert panels on the clinical strategy of the device(s) per Article 61 (2), please provide a copy of the opinion and reference.

(b) Clinical Development Plan for the device.

- In line with Annex XIV Part A, a clinical development plan should be provided for the device that describes progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations, and a PMCF.

- For legacy devices (and if applicable) please provide a justification within the clinical development plan for any deficiencies as described in the first indent noting any reference to PMCF activities that are ongoing or reference to the PMCF Plan as described in Annex XIV.

- The clinical development plan should be part of the Clinical Evaluation Plan.

(c) Clinical Evaluation Plan for the device.

- A clinical evaluation plan should be provided for the device that is aligned to Article 61 (12) and Annex XIV Part A.

The Clinical Evaluation Plan should outline at a minimum:

- An identification of the general safety and performance requirements that require support from relevant clinical data.

- A specification of the intended purpose of the device.

- A clear specification of intended target groups with clear indications and contra-indications.

- A detailed description of intended clinical benefits to patients with relevant and specified clinical outcome parameters.

- A specification of methods to be used for examination of qualitative and quantitative aspects of clinical safety with clear reference to the determination of residual risks and side-effects.

- An indicative list and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device.

- An indication how benefit-risk issues relating to specific components such as use of pharmaceutical, non-viable animal or human tissues, are to be addressed; and

- A clinical development plan (as mentioned in point (b) above).

Note: A legacy device may have a clinical evaluation plan that is different to a new device under MDR. MDCG 2020-6 Appendix II describes the expected content of a legacy device clinical evaluation plan.

(d) Clinical Evaluation Report for the device.

NOTE: A Clinical Evaluation Report is always required for the device per Article 61 (12).

The Clinical Evaluation Report should provide the following information at a minimum:

- Specification of the frequency of CER updates and provision of this rationale.
- CVs and Declaration of Interests of all individuals conducting / approving the clinical evaluation and ensure these are appropriate for the device under evaluation (e.g. including an end user of the device, e.g. medical professional).
- The literature search protocol, the literature search report, the list of databases used, and a copy of all literature articles selected and analysed within the clinical evaluation report, ensuring these have been performed within appropriate timelines.
- If clinical investigations have been performed, the following documentation is required:
    - Clinical investigation plan(s).
    - Completed clinical investigation report, signed by the principal investigator(s).
    - Evidence of communication and no objections with the ethics committee.
    - All regulatory approvals of the clinical investigation (from all countries, including outside of EU).
    - Investigator's brochure.
    - Sample of the informed consent.
- If any deviations to the protocol have been applied, then justifications/acceptance of these deviations should be provided with copies of original and changed protocols.
- If a pre-market clinical investigation has been conducted, please ensure: the final report demonstrates that requirements for all safety and performance endpoints have been met; there are no open clinical investigations relevant to your devices with endpoints related to safety or performance claims; study locations are included in the pre-market clinical investigation.
- When clinical investigations are conducted outside the EU: provide an analysis whether results are transferable to the European population, consider the relevance of ISO 14155 and whether the results are publicly available.
- Statistical Analysis Plans (SAP) - a clear description must be provided of the statistical tools, techniques, analyses used in the design and conduct of clinical investigations, and analysis of clinical data within the overall clinical evaluation.
- The rationale if clinical investigation has not been performed for Class III and implantable devices per Article 61 (7).

- Information on public registration in EUDAMED of clinical investigations conducted.

- With respect to Regulation (EU) 2017/745, including EUDAMED single registration number, when available, or a rationale if clinical investigations are not performed under Regulation (EU) 2017/745 and are not publicly registered or published.

- All Competent/Regulatory Authority correspondence (from all countries, including outside of EU).

- If the clinical evaluation of the device relies on a justification of equivalence of comparative devices: detailed demonstration of equivalence regarding technical, biological and clinical characteristics and information on all differences between it and the comparable devices relative to intended use, technical, or biological factors.

- Justifications for allowable differences should be presented with scientific evidence and this evidence should be provided separately.

- For Class III and implantable devices: if the proposed equivalent device is produced by a different manufacturer, a copy of the signed contract between the two manufacturers that explicitly allows full access to the equivalent marketed device's technical documentation on an ongoing basis shall be provided and evidence that the equivalent device is MDR certified.

- For devices incorporating medicinal substances, a conclusion on the risk/ benefit of adding the ancillary substance to the device should be included. If the device covers multiple strengths or indications, this should cover all variants.

Note: MEDDEV 2.7/1 Rev. 4 Section A9 'Clinical evaluation report - proposed table of contents, examples of contents' provides a helpful layout on the expectations of the content of a clinical evaluation report.

(e) Post Market Clinical Follow Up (PMCF) Plan.

The content of the PMCF plan should consider at a minimum the requirements of Annex XIV Part B and the template provided in MDCG 2020-7 by providing the following information:

- General PMCF methods and procedures to be applied (or justification for absence of any activities as mentioned in Annex XIV Part B 6.2 (a)).

- Specific PMCF methods and procedures to be applied (or justification for absence of any activities as mentioned in Annex XIV Part B Part B 6.2 (b)).

- If the PMCF plan includes a PMCF study, then the full detailed study protocol should be provided with statistical analysis plans, and a clear statement from the manufacturer indicating commitment to the PMCF plan.

- If the PMCF plan does not include a PMCF Study, then a justification should be provided per Annex III of the MDR.

(f) Post Market Clinical Follow Up (PMCF) Evaluation Report.

The content of the PMCF Evaluation Report should be aligned to MDCG 2020-8 and should consider the following points:

- Include any information and reports from PMCF activities previously carried out.

- The PMCF evaluation report should include all general PMCF methods and procedures applied (Annex XIV Part B 6.2 (a)) and specific PMCF methods and procedures applied (Annex XIV Part B Part B 6.2 (b)).

- The report should identify the PMCF studies and stratify the data to the applicable indication of use and further stratified to the models/variants that have been included. In cases with multiple indications, sizes and variants - tabulated data is preferable.

(g) Summary of Safety and Clinical Performance (SSCP) Report.

Per Article 32 of the MDR, all Class III and Implantable devices (excluding custom made devices) require an SSCP.

The content of the SSCP Report should be aligned to the layout template and guidance provided in MDCG 2019-9 and should consider the following aspects:

- All information provided in the SSCP must be traceable to the technical documentation.

- Please confirm with your notified body the languages preference for validation of the SSCP.

- The SSCP should be in pdf format, printable and searchable and follow the template provided in MDCG 2019-9.

- The SSCP should be updated annually (as per Article 61), if indicated, over the lifetime of the device as needed, and updates should be defined in the Post-Market Surveillance Plan.

- For Class IIa implantable and Class IIb implantable WET (Well-Established Technologies) devices, the MDR allows notified bodies to choose representative devices from each device category or generic device group, respectively, for the assessment of Technical Documentation. The SSCPs for such devices chosen as the representative samples will be validated by the notified body as part of the technical documentation assessment for those devices. MDCG 2019-9 requires that notified bodies also upload the unvalidated SSCPs of the devices that were not chosen as representative devices (but are part of the same device categories or generic device

groups) to EUDAMED and, therefore, these will need to be provided before certificate issue.

For Class III devices that are intended to be used directly by a patient or implantable devices that require an implant card (per article 18) then a patient/layperson version of the SSCP is always required. For all other devices the availability of a patient/layperson version SSCP should be considered. If it is still decided that a patient version/layperson is not applicable, then a robust justification must be provided.

For the patient/layperson version SSCP ensure:

- Appropriate patient/layperson terminology is used throughout the document in addition to stylistic recommendations.
- Evidence is provided of an appropriate validation technique of the layperson test.
- The layout template and guidance provided for the patient/layperson in MDCG 2019-9 is applied and the provided example statements have been considered.

Post Market Surveillance

The submission should contain the following documentation on post-market surveillance:

- The post-market surveillance plan (in line with MDR Article 84).
- The post-market surveillance report (in line with MDR Article 85) for Class I devices.
- Periodic safety update report (in line with MDR Article 86) for Class IIa, IIb, III devices.
- PMCF plan (as detailed in Part B of Annex XIV), PMCF study protocols and PMCF evaluation report (or a justification as to why a PMCF is not applicable).
- A copy of the Post Market Surveillance procedure and the procedures put in place to ensure compliance with the obligations resulting from the provisions on vigilance set out in Articles 87 to 92.

The manufacturer should also provide the following post market surveillance data for the last 5 years:

- Market History.
- Worldwide and EU sales volumes.
- Complaints data and trend analysis.
- Vigilance data and trend analysis.
- Data from clinical studies, including post-market clinical follow-up and registries and data from other PMS sources.
- Modifications made and/or corrective actions taken following the incidents reported and revisions made to the risk management file.