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Guidance on technical documentation and Design Dossiers for non-active medical devices

Whereas the term **"technical documentation" or "technical file"** is used for medical devices of Class I, Class IIa, and Class IIb, the term **"Design Dossier"** is used for Class III products.

Technical documentation is retained on the premises of the manufacturer or the authorized representative for potential review of competent authorities and notified bodies. Part B of the technical file may be available at the manufacturer only, whereas Design Dossiers have to be submitted to the notified body for review prior to CE marking of the product (use form "MDD application for CE conformity assessment"; MED_F_03.15; **http://www.tuev-sued.de/industry-and-consumer-products/download-center/applications)**. We will assign a project coordinator who will entrust one or more further experts with the review of particular modules. All experts will be at your disposal directly or indirectly through the project coordinator. After successful review, the notified body will issue a design examination certificate according to Annex II.4 of the Council Directive 93/42/EEC concerning medical devices (MDD) certifying compliance with the relevant provisions of Annex I of the MDD.
Article 5 MDD describes the consideration of the European harmonized standards by the manufacturer in order to demonstrate compliance with the Essential Requirements. This aspect is even more important as international standard organizations have adopted European norms (and vice versa), and demonstrating compliance with these standards could be very helpful in international mutual recognition of the CE marking process.
It is not necessary to include all those documents in the Design Dossier which have already been subject to an ISO/EN/MDD audit by a notified body. Examples of documents not necessarily to be included are quality manuals and related lower level documents.
If the manufacturer of a medical device provides detailed information according to the checklist described below, the requirements of the Directive are appropriately addressed.
This is even more important in case a competent authority or another notified body wishes to review the documentation. Generally, the information should be provided as conclusions, summaries, reports, tables, or flowcharts (with reference to the full documentation in the Essential Requirements checklist).
Special care should be taken to ensure that **any information is consistent throughout the technical file/Design Dossier** (intended use in the product description, instructions for use, risk management file, clinical evaluation report, etc.).
A complete pagination of the technical file/Design Dossier or another type of control mechanism is necessary, e.g. a revision control of each section. A hard copy of the documentation and an electronic version are required to achieve an appropriate review time. In general, design changes described in the MDD (93/42/EEC as amended by 2007/47/EC), Annex II.4.4 shall be reported to the notified body. Please use form "MDD application + Appendix D change notification" **(http://www.tuev-sued.de/industry-and-consumer-products/download-center/applications)** in order to ensure conformity with the requirements defined in Annex II.4.4 and in order to ensure that the Design Dossiers retained in the notified body's archive are complete **and up-to-date.**

Furthermore, at least one **sample of the device** should be provided.
For **all data SI units of measurement** shall be used.

Please note: Technical documentation/Design Dossiers that accurately conform to the below guidance can be reviewed more efficiently!

In this regard it is recommended to compile a Design Dossier or technical file as follows (see also NB-MED/2.5.1 and GHTF document SG1 (PD)/N011R20: STED).

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PART A: Technical documentation/Design Dossier

1. Table of contents

Content of both parts A and B.

2. Introduction

- Revision history of the technical documentation/Design Dossier: Change notifications, revision numbers, and approvals of all documents including all amendments
- Regulatory information:
  -Name, postal address, notified body, certifications (valid copies attached!) of:
    - Manufacturer (including contact person)
    - OEM and critical component suppliers, subcontractors for outsourced critical processes (e.g. contract sterilizer)
    - European representative (if applicable)
  - Product and accessory classification, rule according to MDD, Annex IX (including bullet point chosen), and classification according to EN ISO 10993-1, Annex A.1
  - Conformity assessment route chosen
  - Universal Medical Device Nomenclature System (UMDNS) and/or Global Medical Device Nomenclature (GMDN) code
  - Product history: Approvals (e.g. FDA 510(k) or PMA clearance), market release, status of any pending request for market clearance; items sold, countries in which product is marketed
- Brief description of the product:
  - Intended use, model names, configurations, variants
  - Accessories for the product, integral parts of the package
  - Applied standards (list or table including the full title, identifying numbers, date, and the organization that created the standard). **Note:** Please make sure to use current standards only or provide a gap analysis and rationale.
  - Rationale if applicable standards or parts thereof have not been considered
- Brief description of the development process:
  - Name, postal address of design center
  - Certification status of design center
  - Flowchart of the development process or process description (e.g. standard operating procedure, SOP)
  - Design input/output, design control, design verification, design validation

3. Design Dossier/technical documentation summary information (reference to supporting documents filed in part B)

- Comprehensive description of the system and each functional component of the device and the related accessories including utilized materials or ingredients (animal/human origin, drug-device combination), packaging, method of sterilization, shelf life, combination with active medical devices. The description should be supported by diagrams, photographs, or drawings, as appropriate.
- Basic scientific concepts that are fundamental for the device including medical, biological, chemical, and physical background information
- In case of a change notification: Description of all changes in comparison with the previous design or manufacturing process (e.g. tabular format considering all chapters/modules of the list of contents on page 2)
- Summary of the essential data and results as detailed in part B
- Information as provided in the instructions/directions for use/manual (detailed in part B): Intended use, indications, contraindications, warnings, adverse events, operation, and use of accessories
- Planned changes

- Summary description of the manufacturing process (including a clear description of interfaces to outsourced processes involved)
- Any other important safety/performance-related information

This structure enables efficient project planning and management. Part A can be used for a prereview in order to instantly notify the manufacturer of open issues or in case particular aspects are not covered in the Design Dossier.

PART B: Annexes

1. Essential Requirements checklist

Example:

ER	Applicability	All applied standards (with date of issue)	Compliance demonstrated by (referenced documents)	Location – Section
7.1	Yes	EN ISO 10993-1:2009, EN ISO 10993-5:2009, etc.	Laboratory test reports: - Cytotoxicity (report number and date)	Section 6.1 a) b) c)

See also Attachment I: European norms and standards and other documents supporting technical documentation and Design Dossiers.

2. Risk analysis

The document (risk management file) which describes the result of the risk management process (including risk analysis, evaluation, mitigation, and overall residual risk evaluation, as well as production/post-production information; see EN ISO 14971, Annex B for an overview) should contain at least the following information:

2.1 General information

- Summary
- Purpose of the document including all project phase(s)/life cycle phase(s) for which the risk analysis was performed and reviewed (e.g. design/product, manufacturing process, user/operation); product identification and description; intended use, shelf life
- Risk management SOP and risk management plan
- Reference to risk management policy, standards (EN ISO 14971, EN ISO 22442, parts 1–3 strongly recommended), specification documents, design documents, procedures, protocols, reports, as well as manufacturing and production process information
- Definition of terms, abbreviations, and acronyms
- Participants of the risk analysis team (persons and organizations), their qualification, responsibility, and authority
- **Note:** The risk analysis team shall include a medically knowledgeable and experienced expert in the corresponding field of application.
- **Note:** The risk analysis team in relation to biocompatibility shall include a knowledgeable and experienced expert in the corresponding field of biocompatibility testing.
- **Note:** The risk management plan according to EN ISO 14971 – especially in relation to risk acceptance criteria – has to be defined by the top management under consideration of the estimated production volume to be sold per year and under consideration of regulatory requirements.

- Identification of medical device characteristics that could impact on safety, e.g. according to EN ISO 14971
- If applicable, consideration of data obtained from literature review, usability testing, market surveillance of similar devices, post-market surveillance, or post-market clinical follow-up (PMCF; also related to, for example, change notifications, predicate or otherwise comparable devices): Complaint history, incidents per number of devices sold, analysis of underlying causes and final outcome, corrective and preventive action including proof of effectiveness
- **Note:** In case part of manufacturing is outsourced, the risk analysis of the outsourced production step still needs to be provided.
- Revision history
- Methodology
  - Hazards/hazardous situations in normal condition: Hazard analysis; patient/user-related (top-down approach, e.g. fault tree analysis, table format)
    - Clinical experience and clinical risks
    - Method for identification of applicable hazards; sources of information used
    - Method for determination of the potential causes of hazards; sources of information used
    - System used for the categorization of severity levels (e.g. examples); description of consequences to patients, users, and other persons
    - System used for the categorization of occurrence of each hazard cause (probability estimate, frequency expressed as, for example, “events per device and time”)
    - Method for combination of severity and occurrence to risk level (diagram, graph, formula, etc.)
    - Criteria for risk acceptance (e.g. acceptable, unacceptable) under consideration of the risk management plan and accumulated risks
    - **Note:** If residual risks remain in ALARP region, a rationale is required to substantiate that no further mitigation was possible according to the risk control option analysis.
  - Hazards/hazardous situations in fault condition: failure mode and effects analysis (FMEA); device-related (bottom-up approach), etc.
    - Method for identification of applicable failure modes; sources of information used
    - Method for determination of the potential causes of failure modes; sources of information used
    - System used for the categorization of severity levels; description of consequences to patients, users, and other persons
    - System used for the categorization of occurrence of each failure mode (probability estimate, frequency expressed as, for example, “events per device and time”)
    - System used for the categorization of detectability of each failure mode (criteria for detectability, frequency of in-process testing: 100%, sampling, or no testing, i.e., validated process)
    - Method for combination of severity, occurrence, and detectability to risk level under consideration of the risk definition (see EN ISO 14971; diagram, graph, formula, etc.)
    - Criteria for risk acceptability (e.g. acceptable, unacceptable) under consideration of the risk management plan and under consideration of accumulated risks
    - **Note:** If residual risks remain in ALARP region, a rationale is required to substantiate that no further mitigation was possible according to the risk control option analysis.
- Result (signed and dated documents): Risk management report
  - Hazards/hazardous situations in normal condition: List of applicable hazards; for each hazard (table format in hierarchical structure, if applicable):
    - List of potential worst-case effects (description of consequences to patients, users, and other persons)
    - List of potential causes of hazards as appropriate
    - Estimation of risk before mitigation (severity, occurrence, risk) including decision on acceptability
    - Definition of risk reduction measures including reference to methods (e.g. design, testing, manufacturing) and results of verification (implementation and effectiveness)

- Estimation of risk after mitigation (severity, occurrence, risk) including decision on acceptability under consideration of the risk management plan and under consideration of accumulated risks
- Risk/benefit weighting under consideration of the state of the art

- Hazards/hazardous situations in fault condition: List of applicable failure modes; for each failure mode (table format in hierarchical structure, if applicable):
  - List of potential failure modes
  - List of potential worst-case effects (description of consequences to patients, users, and other persons)
  - List of potential causes of failures (as appropriate)
  - Estimation of risk before mitigation (severity, occurrence, detectability, risk) including decision on acceptability
  - Definition of risk reduction measures including reference to methods (e.g. design, testing, manufacturing) and results of verification (implementation and effectiveness)
  - Estimation of risk after mitigation (severity, occurrence, detectability, risk) including decision on acceptability
  - Risk/benefit weighting under consideration of the state of the art
- New hazards: Assessment of risks associated with new hazards in normal and fault condition generated by risk mitigation measures; corresponding risk reduction, if applicable

- Final judgment, statement of:
  - Completeness of risk evaluation
  - Effectiveness of mitigation measures including a link to the verification documents
  - Overall acceptability of residual risk
  - Signed and dated by the team leader or responsible person

2.2 Usability engineering file

- Documentation according to EN/IEC 62366 in relation to the accompanying documents (IFU, labeling) and use scenario of the medical device
- Comprehensive documentation of usability-related risks of the primary operation functions of the medical device:
  - Risk assessment in normal condition state according to EN ISO 14971 and for foreseeable misuse in relation to the intended use of the device
  - Link from risk management to the usability validation data as evidence for risk verification
- If applicable, market data on use errors including:
  - Number of products sold and complaints received in relation to usability (may be linked to PMCF)
  - Statement if the design of the device in relation to the marketed design has changed
- Usability validation documentation including:
  - Statement on usability verification of the final design
  - Description of worst-case scenarios and frequent-case scenarios of the testing environment and conditions
  - Sampling rationale on amount of users and patients used at validation taking into account the risk reduction stated in the risk management file (shall reflect the occurrence reduction due to the defined risk control measure)
  - Acceptance criteria for pass or fail of the usability study
  - Evidence on the competence of the laboratory conducting the study (including impartiality of the testing personnel)
  - Final conclusion and verifiable feedback to the risk management system

3. Drawings, design, product specifications

- Comprehensive description of the product
- Components and materials: Complete chemical, biological, and physical characterization
- Photographs, blueprints
- If nanomaterials/nanoparticles (with at least one dimension below 100 nm) are utilized in the device, the following characteristics need to be presented:
  - Agglomeration state
  - Aggregation
  - Composition (e.g. chemical composition and structure)
  - Particle size
  - Size distribution
  - Purity/impurity
  - Shape
  - Solubility (hydrophobicity, liposolubility, water solubility)
  - Stability
  - Surface area
  - Surface chemistry
  - Surface charge
  - Coating characteristics
  - Functional characteristics and technical performance specifications such as mechanical characteristics, physical characteristics, electrical characteristics, biological characteristics, chemical characteristics, sterility, stability, packaging, transport, storage, combination with other medical devices, accuracy, sensitivity, specificity of measuring and diagnostic devices, reliability
- Other important descriptive characteristics not detailed above
- Final product release criteria including reference to verification test/validation

4. Chemical, physical, and biological tests

4.1 In vitro testing – preclinical studies

- In general, testing must be conducted to predict the adequacy of the device response to physiological and pathological stresses, undesirable conditions and forces, long-term use, and all known and possible or foreseeable failure modes.
- Testing: Visual, chemical, biological (see also 4.3), physical/mechanical testing (i.e., tensile strength, durability, corrosion, fatigue, long-term stability), efficacy/performance testing
- Simulated use testing:
  - Study objectives
  - Methodology
  - Results
  - Analysis
  - Conclusions including rationale and limitations for selection of the model
- Testing shall be performed on finished products (devices from normal manufacturing and after sterilization).
- Use of semifinished devices, components, or raw materials must be characterized and justified.
- Finite element analysis (FEA), if applicable
- Drug compatibility: Interaction between drug and device (e.g. adsorption)
- Test protocols:
  - Purpose and objective of testing
  - Standard applicability matrix
    - List or table including the full title, identifying numbers, date, and the organization that created the standard

- List of all sections
- Justification, if particular sections are not applicable
- Reference to verification test/validation

- Justification, if applicable standards or parts thereof are not considered; if other methods such as internal standards are used, these methods shall be described in detail.
- Accelerated and real-time aging and simulated distribution (package testing) prior to testing; otherwise, a justification is required.
- Conditions of accelerated aging (formula used to calculate shelf life: e.g. ASTM F 1980)
- For each test:
  - Parameters to be measured and test description including reference to test procedure, if applicable
  - Measuring and testing equipment
  - Calibration arrangements
  - Acceptance criteria
  - Number of test samples including sample size rationale

- Test reports:
  - Deviations and amendments to the protocols and justification
  - Reference to raw data including date, laboratory, location, engineer, testing equipment (device number and calibration date)
  - Statistical analysis
  - Interpretation of data and conclusion(s)
  - Approval signature(s)

4.2 In vivo testing – preclinical studies

- Preclinical **animal studies** used to support the probability of effectiveness in humans.
- Good laboratory practice (GLP) for animal studies
- Objectives, methodology, rationale for selecting the particular animal model including transferability to humans and limitations
- Results, analysis (also statistical) of the functional effectiveness and the device's interactions with animal fluids and tissues, see also 4.3
- Pharmacological, pharmacokinetical, and toxicological studies, i.e., purity, toxicity, ADME (adsorption, distribution, metabolism, and excretion studies, LD_{50}), see also 4.3
- Manufacturer's conclusions

4.3 Biological evaluation

See Med-Info "Biological evaluation"

4.4 Biostability tests

Influence of the biological matrix on the device, i.e.:

- Surface stress cracking on polymers
- Corrosion of load-bearing metal screws
- Coating stability
- See also 4.3

4.5 Microbiological safety, animal origin tissue

- Geographical origin and boarding of animals: Species, country, herd, feeding, age
- Origin of material used/nature of starting tissue:
  - Specified risk material: Organ, tissue, body fluid
  - For TSE-relevant species: If available, certificate of suitability of starting materials with respect to TSE issued by the European Directorate for the Quality of Medicines (EDQM)
- Veterinary controls:
  - Certificate demonstrating conformity with veterinary inspection criteria indicating that the raw material was fit for human consumption
  - Certificate documenting that the applied techniques for stunning and slaughtering were suitable to avoid cross-contamination with specified risk material (references: EN ISO 22442-2, SSC guidelines, EC decisions)
- Risk analysis
  - Risk analysis performed according to EN ISO 14971 and EN ISO 22442-1/-2/-3, including immunological, toxicological, and (chemical/liquid) sterilization risks
- Documentation of significant processing steps
  - Flowchart including the starting material and all intermediate and relevant process parameters such as temperature, duration, and pH value
  - Detailed description of the manufacturing process including all in-process controls
- Procedure for the reduction or inactivation of potentially existing infectious agents
- Documents on the systematic approach to gather information on new relevant zoonoses and infectious agents:
  - Validation study on virus inactivation/elimination including:
    - Current literature survey on relevant zoonoses
    - Information on the production step with potential for inactivation
    - Study protocol (including information on the test article, test organism, rationale for the choice of the relevant or model organism, indicator cell, virus titer, test method, controls, methods for calculating the results, scaling down, interference and cytotoxicity tests)
    - Final test report
    - Raw data
    - Such a study is dispensable if the inactivation potential of the processing step under consideration is well established in scientific literature.
- Slaughtering, transport, and handling
  - Include a statement and respective certificates that the requirements of Regulation 1069/2009 are met, that is: A certificate is required that the animals have received ante- and postmortem inspection by a veterinarian and were deemed fit for human consumption.
  - Traceability, e.g. a lot-wise documentation of individual animals
  - Measures adopted to avoid cross-contamination during slaughter, transport, storage, and manufacturing
- Combination with other medical devices
  - Impact on the materials of animal origin
- Quantity of raw material per medical product
  - Raw material required for one daily dose: Amount (mass in grams) used for production of the single unit equivalent to one daily dose
- Possible number of applications of medical device
  - Number of daily doses
- Route of application
  - Product coming into contact with the central nervous system region, central circulatory system, damaged/breached skin, mucosal membrane, undamaged skin, etc.

- Justification for the use of animal tissues or derivatives in the medical device, including a rationale for the acceptability of the overall (TSE) risk estimate, the evaluation of alternative materials, and the expected clinical benefit

- Clinical benefit
  - Justification for the use of material of animal origin
  - Critical discussion of alternatives (e.g. synthetic, allogenic, autologous, or xenogenic material from non-TSE-relevant species)
  - Unique characteristics of the product under consideration
- Source establishments and/or third-party suppliers for the animal material used; documentation of the contractual agreements and the procedures in place with regard to the auditing of source establishments and/or third-party suppliers for the animal material

4.6 Drug/medical device combination

Considerations for the consultation procedure to the competent bodies of the member states or the European Medicines Agency (EMA) regarding the assessment of usefulness and safety applied to a medicinal substance, which is of ancillary purpose, in a drug-device combination.

- Guidance documents and regulations:
  - 2001/83/EC
  - 2004/27/EC
  - MEDDEV 2.1/3
  - Clinical Safety Data Management (ICH E2)
  - Dose Response Information to Support Drug Registration (ICH E4)
  - Good Clinical Practice (ICH E6)
  - Investigation of Drug Interactions (CPMP/EWP/560/95)
- The documentation for the drug to be consulted should be provided in CTD format. A guideline to the contents is to be found in MEDDEV 2.1/3, part C (see also 4.7)
- Bench testing:
  - Demonstration that the drug and device neither chemically nor physically interact adversely with each other
  - Assessment how the application of the drug and the drug-carrier to the device may affect its fatigue and corrosion properties, coating integrity, durability, and any other relevant product-specific components
- Pharmacodynamics (proof of concept)
- Nonclinical pharmacokinetic testing:
  - In vivo pharmacokinetic studies to quantify the duration of drug exposure
  - Drug concentrations to be measured at local (tissue), regional (organ), and systemic levels in animals
  - In case of very small drug doses, time-release profiles usually suffice to demonstrate safety for human trials.
  - Determination of the quantity of drug remaining on the device
- Preclinical toxicity studies: Dosing studies to establish an efficacy margin between the subtherapeutic dose and the therapeutic dose, and a safety margin between the therapeutic dose and the toxic dose. When polymer of carrier is present, additional controls to evaluate the carrier alone, without the drug, must be included.
- Clinical testing of the active substance if not an approved medicinal product: Additional animal toxicity and human phase I studies are to be expected if the drug component is not approved.
- Clinical data:
  - Clinical pharmacokinetic testing: Human toxicity phase I studies are to be expected to determine the no-observed-adverse-effect level (NOAEL) if the drug component is not approved.

- Confirmatory clinical trials: When the medicinal substance of the combination is known to the competent authority and already registered, and the applicant claims comparative medicinal substance release characteristics, the use of clinical surrogate measures in the setting of a non-inferiority study against an approved device may be acceptable, provided that long-term safety concerns can be clearly ruled out for the claimed target population.
- For further requirements regarding clinical data see section 5.

4.7 Blood derivatives, human tissue/medical device combination

- Human blood derivatives as specified in Annex I of the MDD, section 7.4 – only where the substance is liable to act upon the body with action ancillary to that of the device.
- Guidance documents and regulations:
  - 2000/70/EC
  - 2001/83/EC
  - 2002/98/EC
  - 2004/33/EC
  - Note for Guidance on Plasma-Derived Medicinal Products (CPMP/BWP/269/95)
  - Note for Guidance on Assessing the Risk for Virus Transmission – new Chapter 6 of the NfG on plasma-derived medicinal products (CPMP/BWP/5180/03)
  - Guideline on the Scientific Data Requirements for a Plasma Master File (PMF) (EMEA/CPMP/BWP/3794/03)
  - European Medicines Agency Recommendation on the Procedural Aspects and Dossier Requirements for the Consultation to the European Medicines Agency by a Notified Body on an Ancillary Medicinal Substance or an Ancillary Human Blood Derivative Incorporated in a Medical Device or Active Implantable Medical Device (EMA/CHMP/578661/2010)
  - Note for Guidance on Virus Validation Studies: the Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses (CPMP/BWP/268/95)
- Relevant European Pharmacopoeia monographs
- Guideline on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with regard to vCJD Risk (CPMP/BWP/5136/03)
- CHMP Position Statement on CJD
- The documentation should be provided in CTD format. A guideline to the contents is to be found in MEDDEV 2.1/3 part C:
  - General information:
    - Description of the device (components, intended use)
    - Justification for the use of blood derivatives (intended purpose, suitability of the substance, critical evaluation of alternatives)
    - Critical evaluation of the results of the risk analysis (potential risk in relation to the expected benefit)
  - Qualitative and quantitative particulars of the constituents:
    - Description of the substance
    - Amount included in the device
    - If modifications were introduced, adequate description required
  - Description of method of manufacture:
    - Overall description of the device manufacturing process
    - Process description for the substance
  - Controls of starting materials:
    - Specification of the blood derivative
    - EU Pharmacopoeia to be referenced (if applicable)
    - National references (if applicable)
    - Plasma master file(s)

- Control tests carried out at intermediate stages of the manufacturing process of the medical device:
  - In-process controls (if applicable)
- Control tests on finished products:
  - Qualitative test(s)
  - Quantitative test(s)
- Stability:
  - Desired function to be maintained during shelf life
  - Recommended storage conditions
- Toxicity:
  - Toxicological profile of the substance
  - New substance: Results of toxicity tests (EN ISO 10993)
- Reproductive function:
  - Toxicological profile of the substance
  - New substance: Results of toxicity tests (EN ISO 10993)
- Embryo/fetal and perinatal toxicity:
  - Toxicological profile of the substance
  - New substance: Results of toxicity tests (EN ISO 10993)
- Mutagenic potential:
  - Toxicological profile of the substance
  - New substance: Results of toxicity tests (EN ISO 10993)
- Carcinogenic potential:
  - Toxicological profile of the substance
  - New substance: Results of toxicity tests (EN ISO 10993)
  - To be considered: Genotoxicity, chemistry, duration of exposure
- Pharmacodynamics:
  - Intended action of the substance with regard to the medical device
- Pharmacokinetics:
  - Description of the pattern of local and systemic exposure to the medicinal substance
  - Maximum level and duration of exposure to be considered
  - Is the potential level of exposure a safety concern?
  - New substance: Release characteristics, subsequent distribution, and elimination
- Local tolerance:
  - Relevant results from EN ISO 10993 to be provided
  - Where appropriate: Relevant literature

4.8 Coated medical devices (biomimicry) requirements on performance and product safety to be considered

- Stability of coating in biological matrix
- Microbiological evaluation
- Fibrinogen adsorption
- Platelet adhesion/activation
- Complement activation tests
- Examples:
  - Hydrophilic coating
  - Heparin coating
  - Silver/gold coating
  - Pyrolytic carbon coating
  - MPC/LM coating (lauryl methacrylate phosphorylcholine/lauryl methacrylate)
  - Parylene polymer coating
  - Collagen/gelatine coating

- PEG coating (polyethylene glycol as lubrication)
- Titanium/HA spray coating
- See also 4.3

5. Clinical data

5.1 Clinical report

A clinical report for a medical device calling for CE marking shall fulfill the requirements of MEDDEV 2.7.1. The following hints, which are generally checked during an in-house review of a clinical report, are based on our experience with submitted documentation in the past; they should give additional advice for the demands outlined in MEDDEV.

- Content-related aspects
- The report should contain a technical description as well as a detailed description of the intended use of the device. A pure reference to the technical documentation cannot be regarded adequate.
- Any clinical risk associated with the use of the device and the medical procedure during which the device is used shall be identified and assessed in the clinical report. In that context, the severity of any hazard as well as the probability of occurrence of the harm shall be characterized. A pure reference to the formal risk analysis cannot be regarded adequate.
- The acceptability of any identified risk shall be assessed adequately. Such a process may include a systematic literature review, bench testing, preclinical or clinical studies.
- In case the literature route is used, transferability of device technology used in publications to the device under assessment is often critical.
- **Notes:**
  - In the majority of cases, a pure literature review will not be sufficient. Rather, the equivalence shall be demonstrated.
  - The adequacy of methods used in the discussed publications shall also be taken into account.
- In case a clinical study is performed, attention should be paid to:
  - Fulfillment of requirements outlined in EN ISO 14155-1 and -2
  - Adequacy of study follow-up regarding the evaluation of safety and performance of the device
  - Adequacy of primary and secondary objectives regarding the evaluation of safety and performance
  - Adequacy of inclusion/exclusion criteria regarding the evaluation of safety and performance
  - Adequacy of statistical methods employed, including sample size estimation
  - Intent-to-treat and per-protocol analysis
- Bench tests, preclinical and clinical studies, if used for the demonstration of safety and performance of the device, shall be detailed and discussed in the clinical report. A pure reference to the technical documentation cannot be regarded adequate.
- **Notes:**
  - The adequacy of preclinical or clinical testing is dependent on the novelty of the device or treatment procedure, compared to established devices or methods.
  - It should be taken into account that statistical issues might also be relevant for the assessment of adequacy of such tests.
- In case that equivalence with the current state of the art shall be demonstrated for any medical device calling for CE marking, not only the identified risks of the device itself may be evaluated for the overall risk-to-benefit assessment of the device. Rather, an adequate state-of-the-art review shall be included in the clinical report.
- State-of-the-art review:
  - “State of the art” is understood as detailed description and discussion of all currently available treatment options and medical devices for the same intended use as the device calling for CE marking, reflecting current medical practice and the acknowledged technologies.
  - To document a systematic state-of-the-art review, a protocol for the identification, selection, collation, and review of scientific literature including search databases, search terms, selection criteria, and rationale shall be attached to the clinical report.

- Reasons for believing that all relevant references, both favorable and unfavorable, are included in the review shall be given.
- Also, the acceptability of publications quoted (i.e., reviewed journal, publication year, qualification of the author) should be included in the discussion.

- In case there are comparable or predecessor devices, this clinical experience should also be included in the report.
- The overall risk-to-benefit assessment of the device shall include the comparison of the device under assessment with the established treatment options/medical devices mentioned in the state-of-the-art section.

The author's conclusions shall be substantiated by the presented data:

- Formal aspects
- The quotation index of the referenced literature shall be attached to the clinical report.
- Intended use/indications/contraindications shall be conclusive in the different parts of the documentation.
- Every claimed intended use/indications/contraindications shall be substantiated by the provided clinical data.
- Relevance of the background and expertise of the author of the clinical report in relation to the particular device and/or medical procedure involved shall be demonstrated by a scientific curriculum vitae.
- The data provided in the different parts of the documentation should be consistent (e.g. indications, technical parameters, etc).

5.2 Other documents to be included in the clinical data documentation

- Copies of the publications quoted in the clinical report
- Reports of all bench tests quoted in the clinical report
- Study protocols and study reports in case preclinical or clinical studies were performed. In case a clinical study was performed, the "letter of no objection" from the competent authority as well as the ethics committee's opinion have to be included.
- Instructions for use, including indications, contraindications, risks/side effects/adverse events
- Risk analysis, including clinical risks
- Post-market experience data of predecessor devices, if applicable
- PMCF plan, if applicable

6. Labels and instructions for use (IFU), patient information, advertising materials

- Demonstration of compliance with MDD, Annex I.13, EN 980, EN 1041, EN ISO 15223
- Sample of labels (shipping labels, sterile package labels), instructions for use, patient information
- Submission of labels/IFU in German or English only is acceptable, but verify compliance with European language requirements!
- Label and IFU content shall be consistent.
- Instructions for use:
  - Description of the device
  - Indication for use (disease or condition that the device will diagnose, treat, prevent, cure, or mitigate, including target patient population)
  - Contraindications (disease or condition and patient population for which the device should not be used because the risk of use clearly outweighs any possible benefit)
  - Warnings (specific hazard alert information)
  - Precautions (special care necessary for the safe and effective use of the device, e.g. actions to be taken to avoid effects on patients/users, adverse effects of use or misuse of the device)
  - Adverse events (potential undesirable and serious outcomes under normal conditions)
  - Operation (directions for use)

- If applicable: Specifications/variants/individualization of treatment (e.g. procedures, methods, frequency, duration, quantity, preparation), alternative procedure (for diagnosis, treatment, or therapy), patient counseling information, instructions for any procedure the patient is expected to perform, how supplied, storage, accessories, sterilization information, patient registration, magnetic resonance environment, installation and maintenance, requirement of user training prior to use

- Where appropriate, the instructions for use must contain the following particulars:
  - Clause 13.6(h): If the device bears an indication that the device is for single use only, information on known characteristics and technical factors known to the manufacturer that could pose a risk if the device is to be reused
  - Clause 13.6(q): Date of issue or the latest revision of the IFU

7. Manufacturing (description of the manufacturing process)

- Multiple facilities, critical suppliers, contract sterilizer, etc.: Quality assurance certificates issued by an accredited third-party inspection body for each facility
- Flowcharts including inspection and preventive monitoring steps
- Control specifications for incoming critical material/components, in-process controls
- Final product release criteria
- Summary of manufacturing methods (molding, extrusion, chemical processes, assembly, etc.)
- Manufacturing conditions (compliance with, for example, FS 209E, EN ISO 14644, EN ISO 14698)
- Quality management (EN ISO 13485) certificate issued by notified body or other registrar for the manufacturing plant
- EC certificate according to Annex II, 3 (full quality assurance system) for the legal manufacturer
- Labeling control
- Traceability
- Product and environmental bioburden, particles
- Pyrogene testing
- Preventive monitoring of processes (e.g. statistical process control (SPC))
- Viral/prion deactivation steps

8. Package qualification and shelf life

- Physical package qualification
- Performance of the product after real-time and/or accelerated aging
- Shelf life: Maintenance of sterility and performance of a product past its shelf life, for example per:
  - EN 868-2 et seqq., packaging materials for sterilization of wrapped goods
  - EN ISO 11607-1-2 and referenced standards therein
  - ISTA 2A for transport validation
  - Real-time aging
  - ASTM F 1980 Q_{10} – accelerated aging test
- The following documents are required for the evaluation of sterile devices:
  - Summary report according to EN ISO 11607
  - Detailed description of the packaging and packaging materials
  - Supplier certificates
  - Compliance of the packaging material with the proposed sterilization method
  - Biocompatibility of the packaging, if necessary
  - Each test method has to be validated, and a rationale why it was chosen including a rationale for statistical compliance of the sample size has to be provided.
  - Packaging integrity test (including visual inspection, dye penetration test, creep and burst testing, bubble emission testing)
  - Microbial barrier test
  - Labeling compatibility

- For aseptical presentation, if applicable: Peelability and seal strength test
- Real-time aging study
- Accelerated aging study, if applicable
- Shipment simulation test (vibration, drop and roll test): Transport validation report
- Packaging process validation report including definition of the packaging and sealing equipment

9. Sterilization

9.1 Terminally sterilized medical devices

- Ethylene oxide: EN ISO 11138-2, EN ISO 11135, EN ISO 11737, EN ISO 10993-7
- Moist heat: EN ISO 11138-3, EN ISO 17665-1, EN ISO 11737
- Irradiation: EN ISO 11137, EN ISO 11737
- EN 556-1
- Brief description of the installation qualification and validation summary (method shall assure at least a SAL of 10^{-6})
- Process validation report with physical performance qualification and microbiological performance qualification
- Sterilization plant certified by a notified body (EN ISO 13485 with EN ISO 1113x series)
- General information:
  - Reason for validation (initial validation/revalidation, change of product, etc.)
  - Manufacturer (name, address), operator of facility (name, address)
  - Date of validation, approval of validation, date of next approval of validation report validity, date of next validation (if applicable), criteria for revalidation
- Product:
  - Description of the product (if applicable, drawings/samples), evidence for the usability for the respective sterilization method
  - Short description of manufacturing conditions (clean room with classification)
  - If applicable, transportation specification (from the manufacturer to the sterilization facility)
  - If applicable, product family specification of the product with the greatest challenge to the sterilization process („worst-case product“) with rationale; if applicable, evidence by experimental data (link to data)
  - If applicable, average bioburden and bioburden trending data, bioburden recovery, bacteriostasis and fungistasis, endotoxin, objective evidence for validated microbial methods according to EN ISO 11737
  - Statement on functional product qualification
- Load description:
  - Description of the most challenging position; if applicable, evidence by experimental data (link to data)
  - Specification of bioburden with limits and, if applicable, justification of upper limit in relation to endotoxins
- Sterilizer:
  - Cycle name (e.g. vacuum cycle No. 9); sterilizer description (type, manufacturer, volume)
  - If applicable: Preconditioning room (type, manufacturer volume), conditioning (type, manufacturer volume), aeration room (type, manufacturer volume), transportation route through the sterilizer (e.g. at irradiation sources)
- Statement on commissioning/installation qualification:
  - Date of last commissioning, specification/statement that at the time of validation all measurement and control equipment was maintained and calibrated (with date of last maintenance/calibration), specification where data of commissioning can be reviewed
  - If applicable, statement on steam quality

- Specifications of physical performance qualification:
  - Packaging including transportation package and sterilization containers
  - Specification of loading including position in preconditioning, in sterilizer, aeration (including drawings, maps), amount of packed products and, if applicable, process challenge devices
  - Description of the distribution of sensors (thermal, humidity, dosimetry, etc.) including positioning at/in the product/in product load under consideration of the critical positions, description of reference measurement point and relations to its position
- Sterilization cycle description (set-point specification):
  - Sterilization cycle validation approach according to a harmonized standard, e.g. method A, B, C (ethylene oxide), overkill (steam), etc.
  - Preconditioning (if applied):
    - Minimum temperature of the product load at entering, temperature, relative humidity, time, description of conditioning as far as applied, maximum elapsed time between preconditioning and commencement of the process
  - I. Ethylene oxide:
    - Sterilization cycle as defined in EN ISO 11135-1 9.5.4:
      - Temperature, relative humidity, time, concentration of ethylene oxide (including course of pressure, ethylene oxide volume/weight – reduction at exposure), description of the ethylene oxide exposure time, description of flushing and aeration
    - Aeration:
      - Temperature, amount of air exchanges/hour, pressure (if applicable), time
      - Ethylene oxide residuals according to EN ISO 10993-7
    - II. Moist heat:
      - Type of process, temperature, pressure, z-value, F0-value, time, $D_{121°C}$
      - Temperature during holding time, maximum temperature difference, fluctuation of temperature, equilibrium time, F0 measured, chamber leak test
  - III. Irradiation sterilization:
      - Type of process, transportation route through sterilizer, irradiation dose, pass mode, verification dose, verification dose range, accomplished verification dose, amount of samples, assigned dose map including: minimum/maximum dose (and positional data, e.g. drawing/scheme), correlation to worst-case position and routine measurement, dosimeters (type and manufacturer, tracing to national standard calibration institute)
      - If applicable: Conveyor speed, scan height, electron acceleration
      - Special requirements:
        - Sample item proportion (SIP) description, product/load density, product materials, dimension of product and load and its orientation in relation to the irradiation source, sterility testing, allowable maximum dose
- Specifications of microbiological performance qualification (if applicable):
  - Specification of the applied procedure (e.g. method A, B, C for ethylene oxide), specification of the applied bioindicators (BIs), if used strain, lot code, manufacturer, CFU, D-value; if applicable: z-value and conformity to EN ISO 11138; incoming BI inspection after purchase and before release
  - Amount and distribution of the BIs (including positioning in product and use as spore strips and spore suspensions)
  - Description of the extraction of BIs (time of extraction)
  - Times/temperatures between extraction and incubation, storage in-between (if applicable), extraction method
  - Specification of incubation procedure (media, media volumes, incubation time, and temperature); if applicable, results of surviving organisms (method A, sec. 7.2.1.2)
  - If applicable, evidence of suitability of the process challenge device
  - If applicable, endotoxin measurements

- Summary/result of validation:
  - Summary of the physical performance qualification (PPQ has demonstrated that all parameters were in the limits of their specifications; explanations for possible deviations and their impact)
  - Summary of the microbial performance qualification (MPQ has demonstrated a SAL of 10^{-6} was reached; explanations for possible deviations and their impact)
  - Specification of control parameters including limits for routine processing
  - Documented evidence of compliance to the specified ethylene oxide residuals (including also resterilization, if applicable)
- Description of routine monitoring:
  - If applicable, parametric release, amount/distribution of BIs, bioburden
  - Link to essential control parameters/release criteria

9.2 Aseptic filling

- EN 556-2
- Validation plan, risk management strategy, identification and evaluation concerning contamination risks, monitoring and evidence/prevention of contamination, definition of aseptic process according to EN ISO 13408-1
- Description of manufacturing environment according to EN ISO 13408-1 (e.g. facility layout, clean-room concept, infrastructure, material and personnel influence, filter systems, clean-room qualification, media, manufacturing aids, environmental and personnel monitoring systems, equipment (qualification, service), personnel (training, cloth change, manufacturing)
- Validation report on three media fill runs according to EN ISO 13408-1

9.3 Reprocessing of resterilizable medical devices

- Documentation according to EN ISO 17664 and EN ISO 15883
- For sterilization and packaging see applicable sterilization and packaging standards in section 8 and 9.1
- IFU: Clear description of the reprocessing process and of related parameters and tolerances: point of use, cleaning, disinfection, packaging, and sterilization
- Risk management discussing:
  - Initial contamination at point of use
  - Explanation for each step of reprocessing how the related contamination is removed (e.g. µg or log reductions) with a clear link to validation documentation giving evidence on compliance
  - Usability-related topics on the reprocessing process
- Validation documentation for each reprocessing step
- Evidence on product conformity after the maximum reprocessing cycle stated: including mechanical testing and biocompatibility of the medical device
- Evidence on validated test methods for life cycle reprocessing simulation and validation (e.g. certification status of applied laboratories)
- If applicable, evidence on the effectiveness of the applied disinfectant to achieve the claimed disinfection at the defined conditions
- If applicable, scientific evidence on the effectiveness of the applied cleaning agent and process to remove prions

10. Measuring function

- 80/181/EWG, MEDDEV 2.1/5
- Sufficient accuracy and stability within appropriate limits of accuracy

11. Combination with other medical devices

- The whole combination must be safe and must not impair the specified performances of the devices (e.g. electrical safety when combined with active medical devices).

12. Compatibility to drugs

- Devices must be compatible with the medicinal products concerned according to the provisions and restrictions governing these products.

13. Other applicable directives and regulations

- Brief description of applicability and summary of compliance with regulation
- Personal Protective Equipment Directive (89/686/EEC)
- Registration, Evaluation, Authorization and Restriction of Chemicals – REACH (Regulation (EC) No. 1907/2006)
- Dangerous Preparations (1999/45/EC)

14. Conclusion

- Summary of the Design Dossier data
- Risk vs. benefit statement
- Date and signature of company representative

15. Declaration of conformity (template)

DECLARATION OF CONFORMITY

MANUFACTURER:	NAME AND ADDRESS
EUROPEAN REPRESENTATIVE:	NAME AND ADDRESS
PRODUCT:	NAME, TYPE, AND/OR MODEL
CLASSIFICATION:	CLASS, RULE ACCORDING TO MDD, ANNEX IX (NOT MANDATORY, BUT RECOMMENDABLE)
CONFORMITY ASSESSMENT ROUTE:	EC DIRECTIVE(S) AND ANNEXES APPLIED

WE HEREWITH DECLARE EXCLUSIVELY UNDER SOLE RESPONSIBILITY THAT THE ABOVE MENTIONED PRODUCTS MEET THE PROVISIONS OF THE COUNCIL DIRECTIVE 93/42/EEC FOR MEDICAL DEVICES.
ALL SUPPORTING DOCUMENTATION IS RETAINED UNDER THE PREMISES OF THE MANUFACTURER.

STANDARDS APPLIED:	LIST OF (HARMONIZED) STANDARDS FOR WHICH DOCUMENTED EVIDENCE OF COMPLIANCE CAN BE PROVIDED
NOTIFIED BODY:	NAME, ADDRESS, AND IDENTIFICATION NUMBER
(EC) CERTIFICATE(S):	EC CERTIFICATE NUMBER(S)
START OF CE MARKING:	DATE, LOT NUMBER OR SERIAL NUMBER OF FIRST CE MARKING
PLACE, DATE OF ISSUE:	NAME OF CITY, DATE
SIGNATURE:	_____
	NAME POSITION (FUNCTION)

Attachment I

Example: European norms and standards and other documents supporting technical documentation and Design Dossiers

Document number	Title of document
EN ISO 13485	Medical devices – Quality management systems: Requirements for regulatory purposes
EN 556	General requirements for medical devices to be designated "sterile"
EN ISO 14155	Clinical investigations of medical devices
EN ISO 11134	Sterilization of health care products – steam sterilization
EN ISO 11135	Sterilization of health care products – EtO sterilization
EN ISO 11137	Sterilization of health care products – radiation sterilization
EN ISO 10993, part 1	Biological testing of medical devices – general requirements
EN ISO 10993, part 5	In vitro tests for cytotoxicity
EN 980	Terminology, symbols for use in medical device labels
EN ISO 15223	Symbols to be used in medical device labels, labelling and information to be supplied
EN 1041	Terminology, symbols and information provided with medical devices – information supplied by the manufacturer of medical devices
EN ISO 14971	Application of risk management to medical devices
EN 868-2 to -10	Packaging for terminally sterilized medical devices
EN ISO 11607-1	Packaging for terminally sterilized medical devices – requirements for materials, sterile barrier systems and packaging systems
EN ISO 11607-2	Packaging for terminally sterilized medical devices – validation requirements for forming, sealing and assembly processes
EN ISO 14644	Cleanrooms and associated controlled environments
EN ISO 14698	Cleanrooms and associated controlled environments – biocontamination
USP	United States Pharmacopeia
Ph. Eur.	Pharmacopeia Europaea
EN 45014	General criteria for supplier's declaration of conformity
MEDDEV 2.12/1	Guidelines on a medical device's vigilance system
NB-MED/2.5.2/Rec2	Reporting of design changes and changes of the quality system
MEDDEV 2.7.1	Evaluation of clinical data
MEDDEV 2. 1/3	Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative

See also ISO 16142: Medical devices – guidance on the selection of standards in support of recognized essential principles of safety and performance of medical devices.

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