Guidance Technical Documentation and Design Dossiers forNon 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 the class III products.

Technical Documentation are retained in the premises of the manufacturer or the Authorized Representative for potential review of Competent Authorities and Notified Body. 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 are at your disposal directly or indirectly through the project coordinator. After successful review, the Notified Body issues a design examination certificate according to Annex II.4 of the Council Directive certifying compliance with the relevant provisions of Annex I of the MDD.

Article 5 of the Council Directive describes 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 documents in the Design Dossier which have already been subject to an ISO / EN / MDD Audit by the Notified Body. Examples of documents not necessary 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 flow charts (with reference to the full documentation in the Essential Requirement checklist).

Special care should be taken to ensure that ***any information is consistent throughout the Technical File/Design Dossier*** (e.g. Intended Use in product description, Information 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. 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 the Annex

II.4.4 and in order to ensure that the Design Dossiers retained at 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.

Important hint: 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):

PART A: Technical Documentation / Design Dossier

1. Table of Content
2. Introduction
3. Design Dossier/Technical Documentation Summary Information

PART B: Annexes

1. Essential Requirements Checklist
2. Risk Analysis
3. Drawings, Design -, Product - Specifications
4. Chemical, Physical and Biological Tests
4.1 In Vitro Testing - Preclinical Studies
4.2 In Vivo Testing - Preclinical Studies
4.3 Biocompatibility Tests
4.4 Bio-stability Tests
4.5 Microbiological Safety, Animal Origin Tissue
4.6 Drug / medical device combination
4.7 Blood Derivates, Human Tissue / medical device combination
4.8 Coated Medical Devices
5. Clinical Data
6. Labels and Instructions for Use
7. Manufacturing
8. Package Qualification and Shelf life
9. Sterilization
10. Measuring Function
11. Combination with other Medical Devices
12. Compatibility to drugs
13. Other applicable directives and regulations
14. Conclusion
15. Declaration of Conformity (Draft)

PART A: Technical Documentation / Design Dossier

1. Table of Content

Content of both Parts A and B

2. Introduction

- Revision history of 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:
    - the manufacturer (incl. 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
  - UMDNS- and/or 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 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 Centre
  - Certification status of Design Centre
  - Flowchart of the development process or process description (e.g. 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 material or ingredient (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 form the fundamentals 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 section B): Intended Use, Indications, Contraindications, Warnings, Adverse events, Operation and use of accessories
- Planned changes
- Summary description of 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 pre-review 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:

E.R.	applicability	all applied standards (with date of issue)	compliance demonstrated by (referenced documents)	location - section
7.1 (text)	yes	EN ISO 10993 -1:2009 -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 (including risk analysis, evaluation, mitigation and overall residual risk evaluation and production/post production information see EN ISO 14971 fig. B1 for an overview) process 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 Scope (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 part 1 -3 strongly recommended), specification documents, design documents, procedures, protocols, reports, manufacturing and production process information
- Definition of terms, abbreviations and acronyms
- Participants of the risk analysis team (persons and organisations), their qualification, responsibility and authority.
- Note: the Risk Analysis shall include a medical knowledgeable and experienced expert in the corresponding field of application.
- Note: The Risk Analysis 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 (also related to e.g. 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, still the risk analysis of the outsourced production step 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 categorization of severity levels (e.g. examples); description of consequences to patients, users and other persons
    - System used for categorization of occurrence of each hazard cause (probability estimate, frequency expressed as e.g. 'events per device and time')
    - Method for combination of severity and occurrence to risk level (e.g. diagram, graph, formula)
    - 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 rational is required to substantiate that no further mitigation was possible according to risk control option analysis.
  - **Hazards / hazardous situations in fault condition**: e.g. FMEA; device related (bottom-up approach)
    - 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 categorization of severity levels; description of consequences to patients, users and other persons
    - System used for categorization of occurrence of each failure mode (probability estimate, frequency expressed as e.g. 'events per device and time')
    - System used for 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, e.g. diagram, graph, formula)
    - 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 rational is required to substantiate that no further mitigation was possible according to 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)
  - 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 EN /IEC 62366 in relation to the accompanying documents (IFU, labelling) 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” acc. 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:
  - Amount product sold and complaints received in relation to usability (may be link to post market clinical follow up)
  - Statement if the design of the device in relation of the marketed design has changed
- Usability validation documentation including:
  - Statement on usability verification of the final design
  - Description of worst case scenario and frequent case scenario 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 competence of the laboratory conducting the study (including impartiality of the testing personnel
  - Final conclusion and verifiable feedback into 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

- Functional characteristics and technical performance specifications such as mechanical, physical, electrical, biological, chemical, 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 device response to physiological and pathological stresses, undesirable conditions and forces, long-term use and all known and possible or foreseeable failure modes
- Testing: e.g. visual, chemical, biological, physical/mechanical testing (i.e. tensile strength, durability, corrosion, fatigue, long term stability), efficacy / performance testing, simulated use
- Testing shall be performed on finished product (devices from the normal manufacturing and after sterilization)
- Otherwise, use of semi-finished devices, components, or raw materials must be characterized and justified
- Finite Element Analysis 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 ageing and simulated distribution (package testing) prior to testing. Otherwise a justification is required
  - Conditions of accelerated ageing (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

Pre-clinical **animal studies** used to support the probability of effectiveness in humans

- Good Laboratory Practice (GLP 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
- Pharmacological / pharmacokinetical / toxicological studies i.e. purity, toxicity, ADME (adsorption, distribution, metabolism, elimination studies, LD_{50})
- Manufacturer's conclusions

4.3 Biological Evaluation

The structured biological evaluation program within the risk management process shall comprise the following:

- **Biological evaluation plan**

  - Purpose of the document and all applied standards
  - Scope, Description of the medical device
    - Categorization of the medical device based on EN ISO 10993-1: Table A1 according to:
      - Nature of body contact
      - Contact duration
        (The category defines which effects need to be considered at least)
    - List of components/materials having direct or indirect body contact:
      - Properties and characteristics of the finished product
      - All materials used in the manufacturing process, including auxiliary materials, additives, process contaminants and residues, leachables, degradation products, other components that do interact with the final product, etc., or reference to the applicable section of the Design Dossier
      - Where appropriate, mention suppliers (Note: Re-evaluation is necessary if source or specification of the materials used change.
      - Where appropriate, define total surface area contacting the body or body fluids
      - Characterize for the materials used chemical/toxicological/physical/ electrical/morphological/mechanical properties
      - List all known possible biological hazards.
  - Description of tested item(s) (finished device, part of device, raw material):
    - Testing shall be performed on the final product or representative samples taken from the final product or from materials processed in the same manner as the final product (if applicable provide LOT/REF. No., etc.)
    - Rationale for the selection of the sample tested
    - Statement on the sterile state of the test sample. If the test sample was not sterilized, a rationale shall be given why sterilization has no influence on biocompatibility of the final device
    - Assign appropriate tests to the biological effects. (Only such tests shall be performed which lead to evident results)
    - Assure that no residues coming out of packaging may negatively influence the product performance and safety
  - Overview of biological effects to be considered in the biological evaluation:
    - The selection and evaluation of any material or device intended for use in humans requires a structured programme of assessment (refer to EN ISO 10993-1 Fig 1)
  - Justification for biological effects not considered or tests not performed:
    - The quality and the extent of documentation as well as the assessment in regard to the intended use determine whether or not biological tests shall be performed with the final product and to what extent
    - Biological evaluation may include both a study of relevant experience and actual testing. Such an evaluation may result in the conclusion that no testing is

needed if the material has a documented history of use in a specified role that is equivalent to that of the device under design
    - Each device should be examined on its own features. Data may be available from suppliers or in the literature. In this case full transferability is to be demonstrated. Test systems, test sensitivity and concentrations used should be taken into consideration
    - Waiving of tests shall be recorded

- **Biocompatibility testing**
    - Qualification of the test laboratory, i.e. accreditation
    - Testing should be conducted according to appropriate good laboratory practices followed by evaluation by competent informed persons
    - For qualitative data: acceptance criteria

- **Biocompatibility test reports** (copies)
    - For qualitative data/results: interpretation
    - Positive results – What to do?
        - Verification of results
        - Chemical characterization of leachables
        - Overall interpretation of the biological evaluation of the device
        - Relevance of clinical use

- **Biocompatibility evaluation and summary report**
    - Review of available toxicity and prior use data for each material/chemical with body contact (Include where appropriate data on residual contaminants (e.g. cleaning aids), additives, catalysts, solvents used in the synthesis, sterilization agents and other processing chemicals, mould release agents, residual monomers, degradation products, experience from clinical use, etc.)
    - Toxicological risk assessment of leachables (EN ISO 10993-17)
    - Critical evaluation of the literature review (Annex C)
    - Compilation of tests performed in tabular form - Example:

Test	Report No. Report date.	Result
Cytotoxicity test - MTT	XY yyyy-mm-dd	In this study under the given conditions no substances with significant cytotoxicity (leading to a cell growth inhibition of more than 30%) were released from the test item

    Further relevant information on the tests:
        - Test sample (part tested) e.g. catheter shaft or tip, balloon, whole device
        - Specification (polymer type, supplier, trade name, additives) e.g. PUR, Pellethane 2363-90A, 20% $BaSO_4$
        - Status of test material (final product, sterile)
        - Type of body contact e.g. circulating blood
        - Contact duration e.g. limited contact duration (≤ 24 h)
        - Standard/norm e.g. EN ISO 10993-5: 2009
        - Extract preparation (medium, surface/mass to volume ratio, temperature, time)
        - Action taken on positive results (see above)
    - Compilation of tests performed in addition
    - The validity of tests performed according to standards which are meanwhile superseded shall be verified by a gap analysis to show whether the product is still in compliance with the valid (revised/new) standards.
    - Overall residual risk/benefit evaluation (Annex B, 2.3)
    - Post-production information (Annex B, 2.5)
        - Biological evaluation report acc. to Annex B.4:
          - summary of the results of the overall evaluation
          - confirm that the risk analysis and risk control have been completed
    - Final assessment of the data reviewed:

        - The documentation should include an appraisal of the toxicological significance of the data. This shall be done by a person with experience in the assessment of the biological safety of medical devices. Suitability of the materials for the intended use should be judged on the basis that there is sufficient information to provide a realistic level of assurance that the risk/benefit ratio is acceptable or toxicological risks are not higher than those currently deemed acceptable for existing devices.
    - Conclusion:
        - A final statement of the manufacturer is necessary. (The manufacturer might conclude that in his opinion, based on the submitted documentation, the product safety is ensured)
    - i.a annual biological risk 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

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 EDQM
- Veterinary controls:
    - Certificate demonstrating conformance 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

- A flowchart including the starting material and all intermediate and relevant process parameters such as temperature, duration, and pH are required.
- A detailed description of the manufacturing process including all in-process controls

Procedure for reduction or inactivation of potentially existing infectious agents

Documents on the systematic approach to gather information on new relevant zoo noses and infectious agents:

- A validation study on virus inactivation / elimination including:
- A current literature survey on relevant zoo noses
- Information on the production step with potential for inactivation
- The study protocol (including information on the test article, test organism, rational for the choice of relevant or model organism, indicator cell, virus titer, test method, controls, methods for calculating the results, scaling down, interference and cytotoxicity tests)
- The final test report
- The raw data

- Such a study is dispensable if the inactivation potential of the processing step under consideration is well established in the scientific literature.

Slaughtering, transport, and handling

- Include a statement and respective certificates that requirements of Regulation 1069/2009 are met, that is: A certificate is required that the animals have received ante and post mortem 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.

A 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 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 B (see also 4.7)
- Bench Testing:
  - Demonstration that the drug and device neither chemically nor physically interact adversely with each other
  - Assessment how application of the drug and 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)
- Non-clinical pharmacokinetic testing:
  - In vivo pharmacokinetic studies to quantify the duration of drug exposure.
  - Drug concentrations should be measured at the local (tissue), regional (organ), and systemic levels in animals
  - In the 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 sub-therapeutic 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 in the setting of a DES 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 Derivates, Human Tissue / medical device combination

- Human blood derivatives as specified in Annex I 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 B:
  - 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
    - The 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 derivate
    - EU Pharm 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 should be considered
- 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 (Bio-mimicry) requirements on performance and product safety to be considered

- Stability of Coating in Biological Matrix
- Microbiological Evaluation
- Fibrinogen Adsorption
- Platelet Adhesion / Activation
- Contact Activation Tests
- Examples:
  - Hydrophilic coating
  - Heparin - coating
  - Silver / Gold - coating
  - Pyrolytic Carbon coating
  - MPC - ML - coating (Methacryloyl Phosphoryl Choline Lauryl Methacrylate)
  - Parylene Polymer coating
  - Collagen / Gelatine coating
  - PEG coating (Polyethyleneglycol as lubrication)
  - Titanium / HA Spray – coating

5. Clinical Data

5.1 Clinical report

A clinical report for a medical device calling for CE-marking shall fulfil 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 the 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 where 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, pre-clinical 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:

- The fulfilment 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, pre-clinical 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 pre-clinical 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 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 favourable and unfavourable 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, and 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 the case pre-clinical 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 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 - 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 on the device of use or misuse)
  - 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 Counselling 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 instruction for use must contain the following particulars:
  - Clause 13.6(h): If the device bears an indication that the device is for single use, information on known characteristics and technical factors known to the manufacturer that could pose a risk if the device were to be re-used.
  - 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
- Flow charts 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 e.g. FS 209E, EN ISO 14644, EN ISO 14698)
- QM (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
- Labelling control
- Traceability
- Product and environmental bioburden, particles
- Pyrogene testing
- Preventive monitoring of processes (e.g. 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 over the shelf-life of a product, e.g. per:
  - EN 868 -2 ff 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
- **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 packaging, if necessary
  - Each test method has to be validated and a rational 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
  - Labelling 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 rolltest): transport validation report
  - Packaging process validation report including definition of the packaging and sealing equipment

9. Sterilization

9.1 Terminally sterilized medical devices

- Ethylene OxideEN 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/re-validation, 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, if applicable date of next validation, criteria for revalidation

- **Product:**
  - Description of the product (if applicable drawings/samples) evidence for the usability for the respecting 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 families 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, bacteristasis 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)
  - Specifications of bioburden with limits and if applicable justification of upper limit in relation to endotoxins
- **Sterilizer:**
  - Cycle name (e.g. vacuum cycle Nr. 9); sterilizer description (type, manufacturer, volume)
  - If applicable: preconditioning room (type, manufacturer volume), conditioning (type, manufacturer volume), aeration room (type, manufacturer volume), Transportation route trough the sterilizer (e.g. at irradiation sources)
- **Statement on Commissioning/Installation Qualification:**
  - Date of last commissioning, specification/statement that at 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 (e.g. thermal, humidity, dosimetry etc.) incl. 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)…)
  - 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 an 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 (incl. 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, if applicable pressure, 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 trough sterilizer, irradiation dose, pass mode, verification dose, verification dose range, accomplished verification dose, amount of samples, assigned dose map including:, min max 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:
      - SIP description (Sample Item Proportion), 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 (incl. 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, if applicable storage in-between, 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 re-sterilization 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 on manufacturing environment according to EN ISO 13408-1 (e.g. Facility lay out, 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 3 media fill runs according to EN ISO 13408-1

9.2 Reprocessing of resterilizable medical devices

- Documentation according 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 related parameters and tolerances: point of use, cleaning, disinfection, packaging and sterilization

- Risk Management discussing:
  - initial contamination at point of use
  - and 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 conformance 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 at the defined conditions the claimed disinfection.
- 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 by combination 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, Authorisation 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 ANNEX IX OF THE MDD* (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(S) NUMBER(S)*
START OF CE-MARKING:	*DATE, LOT NUMBER OR SERIAL NUMBER OF FIRST CE-MARKING*
PLACE, DATE OF ISSUE:	*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 Managements Systems – Requirements for Regulatory Purposes
EN 556	General requirements for medical devices labelled 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 – informations supplied by the manufacturer with 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
Eph	Pharmacopeia Europaea
EN 45014	General criteria for suppliers declaration of conformity
MEDDEV 2.12/1	Guidelines on a Medical Devices Vigilance System, MEDDEV 2.12/1
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.