Guidance Document Technical Files / Design Dossiers Non Active Medical Devices

Product Service

Whereas the expression "***Technical File***" is preoccupied for Medical Devices of class I, class IIa and class IIb, and "***Design Dossier***" for the class III products.
Technical Files are retained in the premises of the manufacturer or the Authorized Representative for potential review of Competent Authorities and Notified Body.

Design Dossiers have to be submitted to the Notified Body for review prior CE-Marking of the product. After successful review, the Notified Body issues a design examination certificate according to the Annex II.4 of the Council Directive certifying compliance with the relevant provisions of the 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. A brief summery of manufacturing processes (flow chart including inspection and preventive monitoring steps) and validation of sterilization processes should be included in the design dossier.

This is even more important if a Competent Authority or another Notified Body wishes to review the documentation.If the manufacturer of a class III device provides detailed information according to the checklist described below, the requirements of the Directive are appropriately addressed.

Generally, the informations should be provided as conclusions, summaries, reports, tables or flow charts (with reference to the full documentation in the Essential Requirement checklist). A complete pagination of the design dossier or another type of control mechanism is necessary. Two copies of the documentation are required to achieve an appropriate review time.

In general, design changes described in the MDD (93/42/EEC), Annex II.4.4 shall be reported to the Notified Body in order to ensure conformity with the requirements defined in the Annex II.4.4 and that the design dossiers retained in the NB archives are complete **and up-to-date**.

TÜV Product Service GmbH
TÜV SÜD Group
Phone: +49 89 5008 43 06
Fax: + 49 89 5008 42 87
Munich Branch
Ridlerstraße 65
80339 Munich
Germany

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The structure of a design dossier or technical file can be broken down in 12 sections as follows:

1. Introduction
2. Essential Requirements Checklist
3. Risk Analysis
4. Drawings, Design,- Product - Specifications
5. Chemical, physical and biological tests
5.1 In Vitro Testing - Preclinical Studies
5.2 Biocompatibility Tests
5.3 Biostability Tests
5.4 Microbiological Safety, Animal origin tissue
5.5 Coated Medical Devices
6. Clinical Data
7. Package Qualification and Shelf life
8. Labels - Instructions for use
- patient informations
- advertising materials
9. Manufacturing
10. Sterilization
11. Conclusion
12. Declaration of Conformity (Draft)

TÜV Product Service GmbH
TÜV SÜD Group
Phone: +49 89 5008 43 06
Fax: + 49 89 5008 42 87
Munich Branch
Ridlerstraße 65
80339 Munich
Germany

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Compilation of Technical File and Design Dossier

Table of Content

Name and postal address of the manufacturer and if applicable the European Representative have to be declared

1. Introduction

- Brief product description
- Product History (i.e. market release, items sold)
    - Intended Use
    - Indication
    - Contraindications
    - Warnings
- Accessories for the product, Integral parts of package
- Regulatory approvals
    - i.e. FDA 510(k) or PMA clearance
- Planned changes
- Classification of the device and accessories according to annex IX of MDD
- Conformity Assessment Route that has been chosen

2. Essential Requirements Checklist

Example:

E.R.	applicability	applied standards	compliance demonstrated by	location - section
7.1 (text)	yes	ISO 10993 -1 -3 -5 etc.	NAmSA test re-ports: - cytotoxicity (#xyz, dtd. 08/07/97 - 90 day implant (#xyz, dtd. 09/10/97	Section 6.1 a) b) c)

See also attachement I: European Norms and Standards and other Documents supporting Technical Files and Design Dossiers.

TÜV Product Service GmbH
TÜV SÜD Group
Phone: +49 89 5008 43 06
Fax: + 49 89 5008 42 87
Munich Branch
Ridlerstraße 65
80339 Munich
Germany

3. Risk Analysis

EN ISO 14971
Table format is acceptable for the Hazard Analysis and FMECA
Post market surveillance (complaint history)
Clinical experience and clinical risks
EN 12442 part 1 -3 and MEDDEV 2.5-8 (Risk Management Animal Tissue)

The document (Risk Management File) which describes the result of the risk analysis process should contain at least the following information:

General information

- Summary
- Purpose of the document
- Scope (which part of the complete system is covered?); product identifica-tion and description; intended use
- List of referenced documents (standards, specification documents, design documents, procedures)
- Definition of terms, abbreviations and acronyms

Methodology

- When (in which project phase) was the risk analysis performed and reviewed
- Participants of the risk analysis team (persons and organisations), their qualification (especially medical knowledge) and responsibility
- Requirements for review of Risk Management activities
- **Hazards in normal condition**: Hazard Analysis; patient/user related (top-down approach)
    - Method for identification of applicable hazards; used sources of in-formation
    - System used for categorization of severity levels
    - Method for determination of the potential causes of each hazard
    - System used for categorization of probability estimates of each hazard cause (frequency in e.g. ‘events per device’)
    - Scheme for combination of severity and probability to risk level
    - Criteria for acceptability of a risk level

- **Hazards in fault condition**: FMECA; device related (bottom-up approach)
    - Method for identification of applicable failure modes; used sources of information
    - System used for categorization of severity levels
    - Method for determination of the potential causes of each failure mode
    - System used for categorization of probability estimates of each failure mode (frequency in e.g. ‘events per device’)
    - System used for categorization of detectability of each failure mode

TÜV Product Service GmbH
TÜV SÜD Group
Phone: +49 89 5008 43 06
Fax: + 49 89 5008 42 87
Munich Branch
Ridlerstraße 65
80339 Munich
Germany

- Scheme for combination of severity, probability and detectability to risk level
- Criteria for acceptability of a risk level

- Procedure to review information in the post-production phase
- Complaint history and data from literature review

- **Result** (signed and dated documents)

  - **Hazards in normal condition:** list of applicable hazards; for each hazard:
    - § List of potential causes (in hierarchical structure, if applicable)
    - § Estimation of risk before mitigation (severity, probability, risk)
    - § Definition of risk reduction measures including reference to methods (e.g. design, testing, manufacturing) and results of verification (effectiveness of implementation)
    - § Estimation of risk after mitigation (severity, probability, risk)

  - **Hazards in fault condition:** list of applicable failure modes; for each failure mode:
    - § List of potential worst case effects and causes (in hierarchical structure, if applicable)
    - § Estimation of risk before mitigation (severity, probability, detect-ability, risk)
    - § Definition of risk reduction measures including reference to methods (e.g. design, testing, manufacturing) and results of verification (effectiveness of implementation)
    - § Estimation of risk after mitigation (severity, probability, detectability, risk)

  - Assessment of risks associated with new hazards generated by risk mitigation measures.

- **Final judgment, statement of:**
  - Completeness of risk evaluation
  - Overall acceptability of residual risk
  - Risk / benefit weighting
  - Signed and dated by the team leader or person responsible.

4. Drawings, Design,- Product - Specifications

- Comprehensive description of the product
- Components and materials
- **Sample of Product**
- Photographs
- Blueprints
- Pre-Production Design Control (brief description)
- QS (ISO EN 9001, ISO 13485) Certificate of design facility
- Final product release criteria including reference to verification test / validation

TÜV Product Service GmbH
TÜV SÜD Group
Phone: +49 89 5008 43 06
Fax: + 49 89 5008 42 87
Munich Branch
Ridlerstraße 65
80339 Munich
Germany

5. Chemical, physical and biological tests

5.1 In Vitro Testing - Preclinical Studies

Bench Testing - chemical and physical testing

- (i.e. tensile strength tests, durability,- corrosion tests, fatigue tests, long term stability) **Note:** for Implants Standards like EN 14630 have to be considered!
- Bench Testing - chemical, biological, pharmacological / pharmacokinetical / toxicological Studies
- i.e. purity, toxicity, ADME (adsorption, distribution, metabolism, elimination) studies, LD_{50})
- Efficacy Tests
- Performance Testing
- Sterilization qualifications

Is the performance of the device adversely affected by the sterilization process?

- Drug Compatibility

Interaction between Drug and Device (i.e. adsorption)

- **Test protocols**
  - Standard applicability matrix
    - List of each item
    - Justification if particular items are not applicable
    - Reference to verification test / validation
  - Justification if applicable standards are not considered
  - Testing performed on finished product (devices from the normal manufacturing and sterilization)
  - Accelerated and real time ageing prior to testing
  - Conditions of accelerated ageing
  - 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 from the protocols and justification
  - Raw data
  - statistical analysis

TÜV Product Service GmbH
TÜV SÜD Group
Phone: +49 89 5008 43 06
Fax: + 49 89 5008 42 87
Munich Branch
Ridlerstraße 65
80339 Munich
Germany

- o interpretation of data and conclusion(s)
- o approval signature(s)

5.2 Biocompatibility Tests

- Applied standard
  - mention the relevant standards here
- Categorization of the device
  - Intended use
  - Nature and duration of body contact
  - The category defines the tests to be performed (ISO 10993-1, table 1)

Listing of components/materials having direct or indirect body contact

List the contact materials here or refer to the applicable section of the design dossier which contains the materials listing
- Where appropriate define total surface area contacting the body or body fluids
- Statement on the test samples used (final product, component, raw material, sterile state)

- Overview of tests performed
  - Description and justification for tests performed
- Justification for tests not performed
  - Literature data, references, existing clinical experience
- Conclusion
  - Final statement of the manufacturer; that in his opinion, based on the submitted documentation, the product safety is ensured

Test results (reports) need to be submitted or compiled in a tabular form:

- Qualification of the test laboratory (accreditation)
- Test sample
  - part tested (e.g. catheter shaft or tip, balloon)
- Specification

  e.g. polymer type, supplier, trade name, additives (e.g. PUR, Pellethane 2363-90A)
- Status of test material

  e.g. raw material, final product, sterile
- Test performed / test system

TÜV Product Service GmbH
TÜV SÜD Group
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Fax: + 49 89 5008 42 87
Munich Branch
Ridlerstraße 65
80339 Munich
Germany

e.g. Cytotoxicity / MEM Elution (L-929 mouse fibroblast cells)

- Extract preparation
  Medium, surface (mass) to volume ratio, temperature, time
  (e.g. MEM, supplemented with 5% calf serum and 2% antibiotics Concentration: 4g/20ml extracted at 37±1°C for 24 hours)
- Standard/norm
  e.g. ISO 10993-5
- Test lab / report number / report date
  e.g. NAmSA / 95B 1245600 / 1998-12-01
- Test result
  e.g. non cytotoxic

5.3 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

5.4 Microbiological Safety, Animal Origin tissue

Viral, Bacterial, Prion Evaluations in case of tissue

- **EN 12442 part 1 - 3** (Animal tissue and their derivates used in the manufacture of medical devices)
- **MED DEV 2.5-8** (Guidelines on evaluation of medical devices incorporating materials of animal origin with respect to viruses and transmissible agents)
- **Directive 2003/32/EC** (applies to material from bovine, ovine, caprine species, deer, elk, cat, and mink only)

The manufacturer has to consider the following points and submit the relevant documentation for evaluation:

- Justification for the use of animal tissues or derivates
- Starting materials, species used
- Assessment of the clinical benefit / potential risk / possible alternatives
- Studies of the elimination / inactivation of BSE/TSE agents and/or alternatively literature research on the subject
- Well documented strategy in risk analysis and risk management and thereby demonstrating that a high level of benefits and safety for the patient has been attained

TÜV Product Service GmbH
TÜV SÜD Group
Phone: +49 89 5008 43 06
Fax: + 49 89 5008 42 87
Munich Branch
Ridlerstraße 65
80339 Munich
Germany

- Consideration of all relevant aspects of the TSE agents and measures to ensure that infection is minimised
- Manufacturers control of the sources of raw materials, finished products, and subcontractors
- The need to audit matters related to sourcing, including third party supplies
- EDQM Certificate, if applicable

5.5 Coated Medical Devices (Biomimicry) - i.e.:

- 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)
- E-Beam Treatment (Cross linkage)
- Titanium / HA Spray – Coating

Requirements on Performance and Product Safety

Stability of Coating in Biological Matrix

- Hydrophilic
- Microbiological Evaluation
- Fibrinogen Adsorption
- Platelet Adhesion / Activation
- Contact Activation Tests

6. Clinical Data

- MDD (93/42/EEC) - Annex 10
- ISO EN 14155-1 and -2
- MEDDEV 2.7.1
- GCP (good clinical practice) requirements

Clinical Studies are required for:

- Complete new device - components, features, methods of action unknown
- Existing device is modified - modification may significantly affect safety and per formance
- New indication for established device
- New materials with body contact
- Device used for a significant longer time

TÜV Product Service GmbH
TÜV SÜD Group
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Munich Branch
Ridlerstraße 65
80339 Munich
Germany

If clinical studies are described, the final study report shall contain:

- Intended use of the device
- Specific aspects of the design and use of the device
- Effects, side effects and undesirable effects of the device
- Assessment of benefit and possible hazard to the patient treated with the device
- Risks should be compared with all alternative methods currently available
- Possible technical solutions minimising the existing foreseeable risks
- Medical procedure or the process in which the device is implemented

Along with the final report of the study the trial protocol, Ethics Committee opinion(s) and comments as well as the authorities "letter of no objection" need to be submitted.

Critical evaluation of all data collected during the clinical investigation

For ongoing studies, a study design, scope of study and expected results (intermediate report) should be described within the clinical section part as well as when final data are available.

Documents to be provided for clinical assessment

- Clinical Report acc. to MEDDEV 2.7.1
- Copies of the literature quoted in the clinical report
- Instructions for use including indications, contraindications, risks / side effects / ad verse events
- Risk analysis including clinical risks
- Post market surveillance data, if applicable
- Study protocol, final study report of pre-clinical or clinical studies, if applicable
- Clinically relevant bench testing reports

Signature of clinical report by medical expert necessary (attach c.v.)

7. 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, i.e per:

- EN 868 -1 ff packaging materials for sterilization of wrapped goods,
- ISO 11607
- ASTM D999 -tests,
- NAmSA Dust Drum Tests
- Real time aging,
- Q_{10} - accelerated aging test

TÜV Product Service GmbH
TÜV SÜD Group
Phone: +49 89 5008 43 06
Fax: + 49 89 5008 42 87
Munich Branch
Ridlerstraße 65
80339 Munich
Germany

Following documents are required for the evaluation of sterile devices:

- o Detailed description of the packaging and packaging materials
- o Supplier certificates
- o Compliance of the packaging material with the proposed sterilization method
- o Biocompatibility of packaging, if necessary
- o Packaging integrity test (including visual inspection and dye penetration test)
- o Microbial barrier test
- o Labelling compatibility
- o Seal strength test
- o Real time aging study
- o Accelerated aging study, if applicable
- o Shipment simulation test (vibration-, drop- and rolltest)
- o Packaging process validation report

8. Labels - Instructions for use - patient informations - advertising materials

- § Demonstrate compliance with Annex I.13, EN 980, EN 1041, ISO 15223 Example of Labels (shipping labels, sterile package labels) - Instructions for use - patient informations

- § Submission of labels / IFU in one language (german/english), only is acceptable, but verify compliance with European Language Requirements!
- § Instructions for Use: Description / Indication for Use / Contraindications / Warnings / Precautions / Adverse Events / Operation

9. Manufacturing

Description of the manufacturing process

- § Flow chart
- § Manufacturing conditions in compliance with i.e. FS 209E, ISO 14644, ISO 14698
- § QS (EN ISO 9001, ISO 13485) certificate from a Notified Body or other registrar for the manufacturing plant
- § EC-certificate according to Annex II, 3 (Full Quality Assurance System)
- § Labeling control
- § Traceability
- § Product and environmental bioburden, particles
- § Pyrogene testing
- § Preventive monitoring of processes (i.e. SPC)
- § Viral- Prion Deactivation steps

TÜV Product Service GmbH
TÜV SÜD Group
Phone: +49 89 5008 43 06
Fax: + 49 89 5008 42 87
Munich Branch
Ridlerstraße 65
80339 Munich
Germany

10. Sterilization

EN 550 series, ISO 11130 series

- § 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 (ISO 9001/2, ISO 13485 / 13488, EN550 series, 11130 series).

11. Conclusion

Summary of the design dossier data
Risk vs. benefit statement

TÜV Product Service GmbH
TÜV SÜD Group
Phone: +49 89 5008 43 06
Fax: + 49 89 5008 42 87
Munich Branch
Ridlerstraße 65
80339 Munich
Germany

12. Declaration of Conformity Template

EXAMPLE 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*
CONFORMITY ASSESSMENT ROUTE:	*ANNEX APPLIED*
WE HEREWITH DECLARE 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*

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Ridlerstraße 65
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Attachment I

Example: European Norms and Standards and other Documents supporting Technical Files and Design Dossiers

Document Number	Title of Document
EN ISO 9001	Quality Systems
ISO 13485	Particular requirements for the application of ISO 9001
EN 550	EtO Sterilization
EN 552	Irradiation Sterilization
EN 554	Sterilization by moist heat
EN 556	General requirements for medical devices _abelled sterile
ISO 14155	Clinical Investigations of medical devices
ISO 11134	Sterilization of health care products – Steam Sterilization
ISO 11135	Sterilization of health care products – EtO Sterilization
ISO 11137	Sterilization of health care products – radiation sterilization
ISO 10993 part 1	Biological testing of medical devices – general requirements
ISO 10993 part 5	In-vitro tests for cytotoxicity
ISO 10993 part 11	Tests for systemic toxicity
EN 980	Terminology, symbols for use in Medical Device labels
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
ISO 14971	Application of risk management to medical devices
EN 868 part 1	Packaging materials and systems for medical devices which are to be sterilized – Part 1: General requirements and test methods
ISO 14644	Cleanrooms and associated controlled environments
ISO 14698	Cleanrooms and associated controlled environments – Biocontamination
USP	United States Pharmacopeia
Eph	Pharmacopoea 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

TÜV Product Service GmbH
TÜV SÜD Group
Phone: +49 89 5008 43 06
Fax: + 49 89 5008 42 87
Munich Branch
Ridlerstraße 65
80339 Munich
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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

TÜV Product Service GmbH
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Munich Branch
Ridlerstraße 65
80339 Munich
Germany