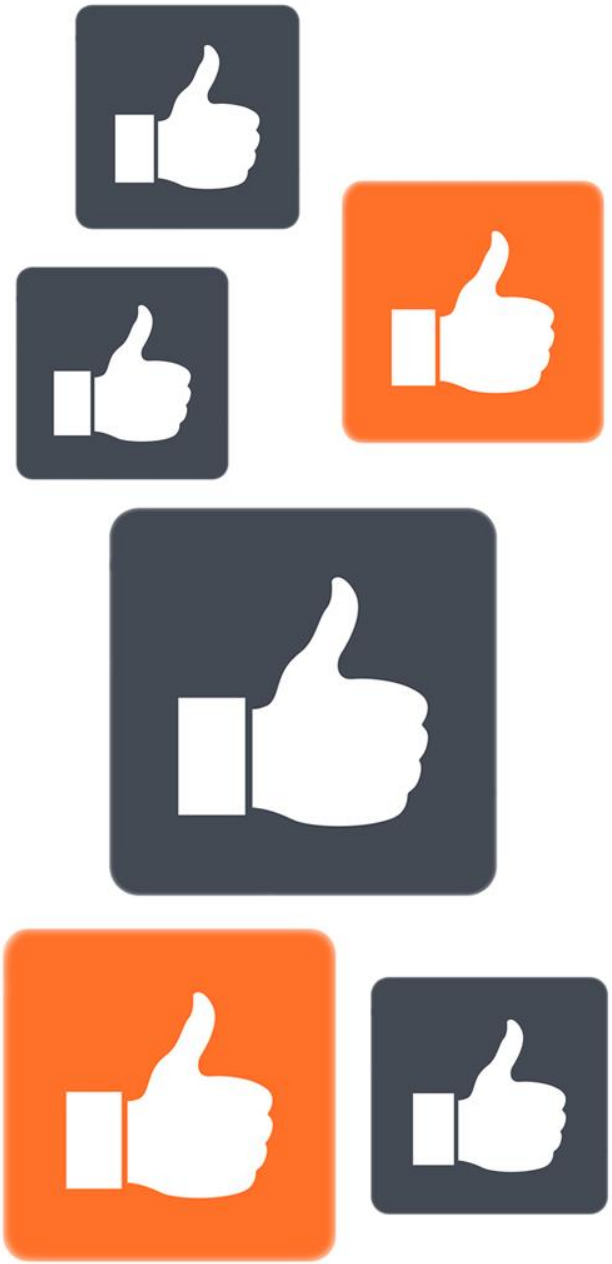

GOOD TECHNICAL DOCUMENTATION

Results of a Dutch study

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Scope

Provide training

- To train QA/RA personnel as well as R&D personnel on the contents of Technical Files
- Improve contents of files required for regulatory submissions

Content

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Industry's practice

(Representative results of a Dutch Study)

- Instead of generating own training materials / guidelines, we will use the results of a study performed in the Netherlands, assessing technical documentation of medical devices.
- Although the study was limited to non-CE-marked devices out of clinical studies, the results are adequate for this basic training.
- Study was performed based on 93/42/EEC, without the amendments done in 2007/47/EC.

For more details see:
RIVM report 360050001/2006
Assessment of technical documentation of medical devices for clinical investigation
B. Roszek1, A.C.P. de Bruijn, A.W. van Drongelen, R.E. Geertsma

RIVM report

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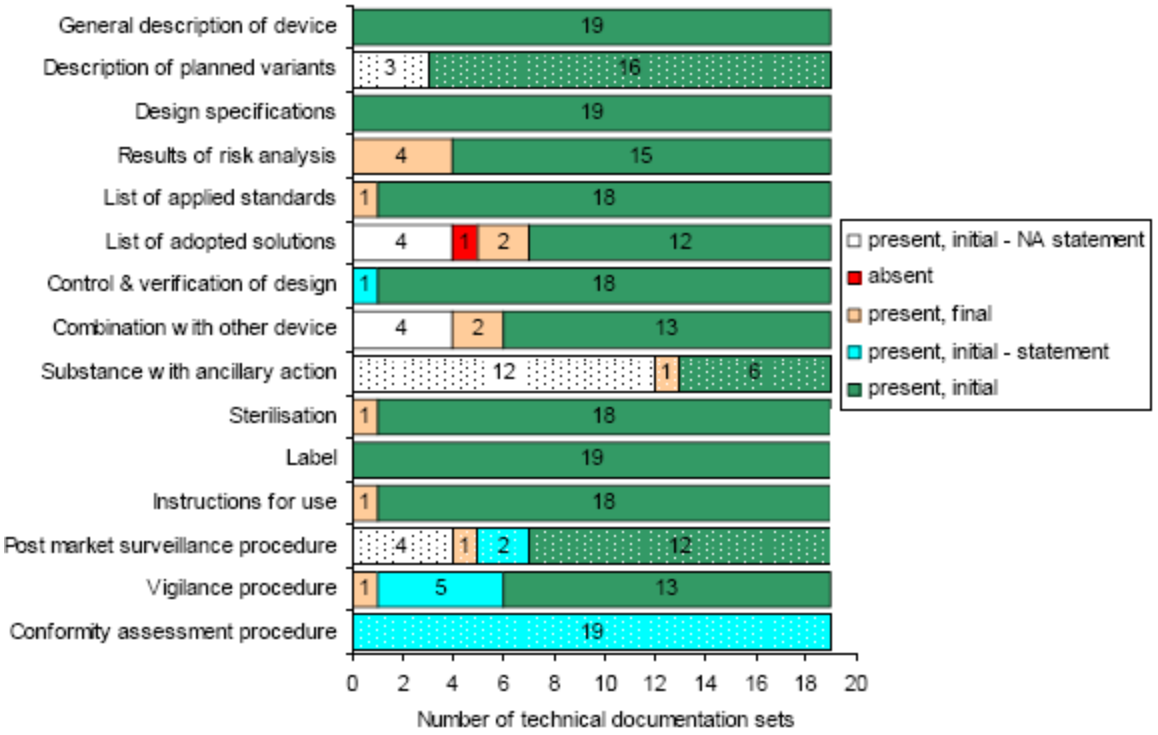
Industry's practice

(Representative results of a Dutch Study)

Availability of documents



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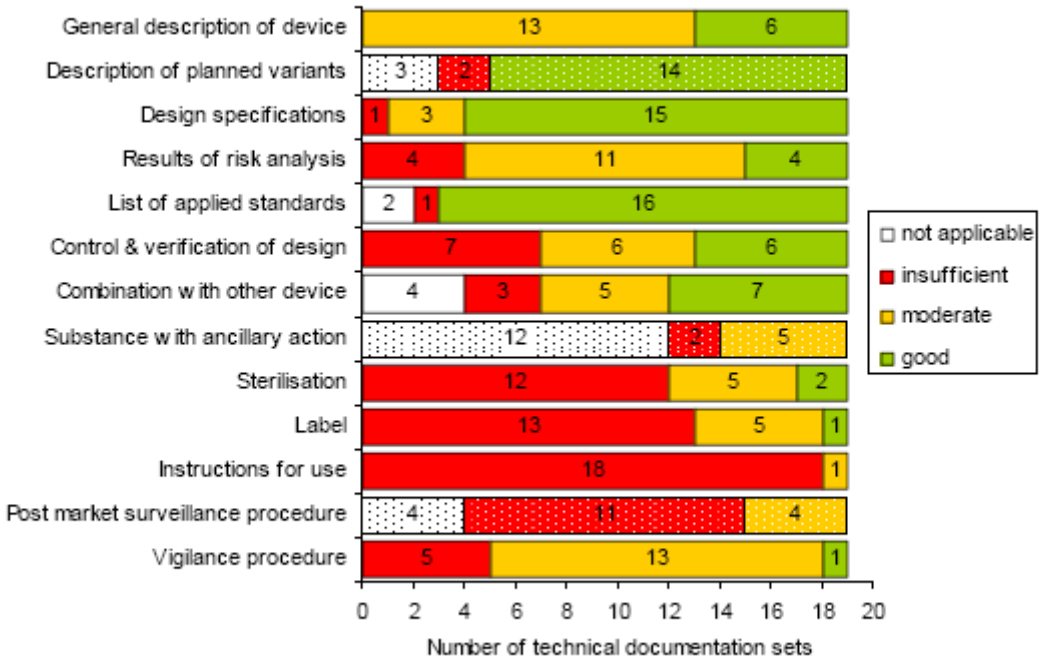
Industry's practice

(Representative results of a Dutch Study)

Quality of documents



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Industry's practice
(Representative results of a Dutch Study)

Results of the risk analysis

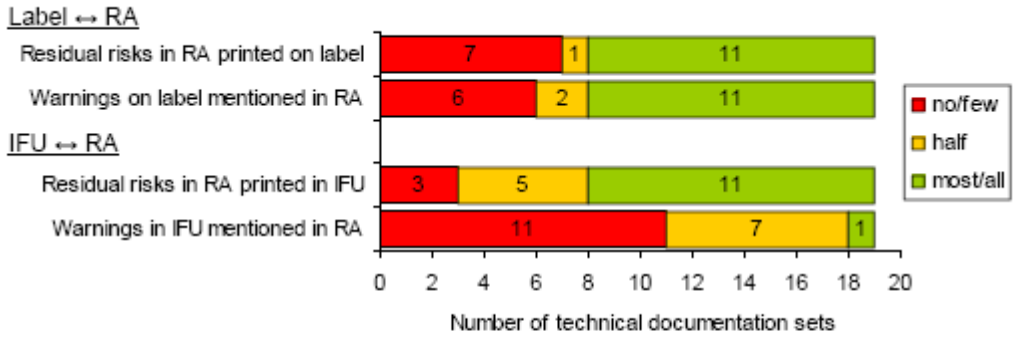

Figure 3. Coherence between information for users supplied by the manufacturer, i.e. label and instructions for use (IFU), and risk analysis (RA). Reciprocal relationships between residual risks/hazards addressed in RA and warnings/precautions mentioned on label or IFU are shown in the upper and lower part, respectively.

Content

Industry's practice (Representative results of a Dutch Study)

Contents of Regulatory files

Conclusions

Checklists

Teamwork

Next steps

Contents of Regulatory Files

General description of the medical device

A good general description of the medical device contains the (generic) name of the medical device, classification of the medical device, physical description of the medical device, schematic drawing / diagram /photograph of the medical device, mode of action, short description of the intended use, and short description of the contraindications, warnings, precautions.

The general descriptions of the medical devices showed no major shortcomings and were addressed well in 6/19 cases. The 'moderate' score for this item merely originated from the classification of the medical device which was often absent in the technical documentation (13/19). Contraindications were mentioned in all except one of the technical documentation sets.Some criteria concerning the general description of the medical device were present in other technical documentation items such as mode of action in the risk analysis, contraindications /warnings / precautions in the instructions for use, and drawings of the medical device on the label. Overall, the structure of this item was not very consistent throughout the sample.

Contents of Regulatory Files

General description of any variants planned

A good description of any variants planned contains information concerning variant characteristics such as physical dimensions, color, weight, etc. In addition, model numbers are mentioned (if applicable).

Variants planned were addressed adequately except for two technical documentation sets lacking a physical description of variants and model numbers. Information on variants was often present in technical documentation items such as the general description of the medical device, design specifications, risk analysis, checklist essential requirements, and / or instructions for use. Noticeably, three manufacturers stated that no variants were planned despite actual descriptions of variants found in the technical documentation.

Contents of Regulatory Files

Design specifications

Good design specifications contain (design) drawing(s) (if relevant), specification of the materials used, biomaterials or components, product specification, and descriptions / explanations necessary for the understanding of the drawing(s) (if applicable).

Design specifications were often addressed adequately (15/19). Shortcomings were due to the absence of (design) drawings, specifications of materials used, and / or product specifications. One (design) drawing did not specify any essential device dimensions or even an indication of the physical size of the medical device.

Some design specifications were present in other technical documentation items, e.g. drawings on labeling, specifications of materials in risk analysis, and product specifications on labeling and in instructions for use. Drawings on labeling were often vague and small. Nevertheless, essential sizes of the medical device were indicated appropriately. Thus, (design) drawings were scored as present if drawings were printed on labeling.

Contents of Regulatory Files

Results of the risk analysis

In a good risk analysis all known or foreseeable hazards are identified, risks arising from the identified hazards are estimated, actions taken to reduce or eliminate the risks are adequate, i.e. control measures are consistently described in line with essential requirement 2 (eliminate or reduce risks as far as possible by inherently safe design and construction, take adequate protection measures including alarms if necessary, in relation to risks that can not be eliminated, and inform users of residual risks / hazards due to any shortcomings of any protection measures adopted).

The results of the risk analysis showed some major (4/19) and many minor shortcomings(11/19). In a major part of the risk analyses several known or foreseeable hazards were not identified. In addition, though to a lesser extent, risks arising from the identified hazards were not estimated. Moreover, a substantial part of the analyses did not mention adequate actions to reduce or eliminate these estimated risks and did not conclude with a justification of residual risks / hazards in relation to anticipated benefits. All risk analyses were according to the standard EN ISO 14971:2000. For the assessment of the technical documentation, the coherence between the risk analysis and the information for users supplied by the manufacturer was also taken into consideration (Figure 3).

Contents of Regulatory Files

List of applied standards

A list of applied standards shall contain products standards (if applicable) corresponding to the list drawn up the assessors.

In all technical documentation sets the applied standards were listed. The standards were either given in a checklist essential requirements (13/19) and / or a separate list (18/19). Only seven checklists essential requirements were dated, ranging from February 2005 up to April 2006. These findings suggest that most manufacturers do not update the checklist essential requirements on a regular basis.

Contents of Regulatory Files

List of adopted solutions

The list of adopted solutions if standards are not applied in full was not assessed. It should be noted that one technical documentation set did not include any solutions to fulfill particular essential requirements at all.

Contents of Regulatory Files

Control and verification of the design

For a good control and verification of the design, test results and procedures are present, and design verification techniques are mentioned.

Control and verification of the design showed several major (7/19) and minor (6/19) shortcomings and, thus, was not adequately addressed. Major shortcomings in the technical documentation sets were due to the absence of tests results in combination with either design verification techniques or procedures. Minor shortcomings were always due to the absence of procedures. One manufacturer stated that a comprehensive quality management system was maintained without submitting any test results, design verification techniques, and / or procedures. This was regarded inadequate. Therefore, control and verification of the design of this particular sample scored 'insufficient'.

Contents of Regulatory Files

Proof of conformity if connected to other medical devices

A good proof of conformity if connected to other medical device(s) contains a description of possible practical combinations and extensive proof.

This technical documentation item showed some major (3/19) and several minor (5/19) shortcomings. Major shortcomings were due the absence of descriptions of possible combinations together with extensive proof. Thus, only a reference document was mentioned in essential requirement 9.1 or the combination was only addressed in the risk analysis without an elaboration or a description of the actual combination. Minor shortcomings were only due to the absence of extensive proof. Noticeably, nine manufacturers stated that their medical devices cannot be connected even though in five of these cases either device combinations were shortly addressed in the checklist essential requirements or in the risk analysis or more detailed descriptions of actual combinations were given in other technical documentation items.

Contents of Regulatory Files

Substance with ancillary action

Good documentation regarding a substance with ancillary action (medicinal substance or blood product) contains a description of the intended purpose within the context of the medical device, source and / or product license (if applicable), method by which the substance is incorporated into the device, tests performed on substance (toxicological, pharmacological, stability, etc.), pharmacovigilance, notification duty for reporting serious adverse drug reactions to competent authorities and / or European Medicines Agency, assessment of substance by national authority or European Medicines Agency.

In seven medical devices a substance was incorporated having an ancillary medicinal action. Remarkably, in none of the technical documentation sets this item was addressed adequately. Present aspects were mainly the intended purpose within the context of the medical device, product source, method of incorporation, and tests performed on the substance. However, pharmacovigilance and notification duty for reporting serious adverse drug reactions competent authorities and / or the European Medicines Agency were always absent. Information on the assessment of the medicinal substance by a national authority or European Medicines Agency was only present in one of the seven technical documentation sets.

Contents of Regulatory Files

Sterilisation

A good description of the sterilization contains (detailed) information on the cleaning process prior to sterilization (if applicable), method of sterilization, parameters of the sterilization process, a summary of sterilization validation data, including the appropriateness of the sterilization method, and packaging material used.

The method of sterilization was always present and included e-beam irradiation, gamma irradiation, ethylene oxide sterilization, steam sterilization, and sterilization by liquid chemicals. Overall, however, sterilization was not addressed adequately in the major part of the technical documentation sets (12/19). Major and minor shortcomings were due to the absence of the information concerning the cleaning process, parameters of the sterilization process, summary of sterilization validation data, and packaging material used.

Contents of Regulatory Files

Label

Good information for the user contains a label in local language (or otherwise in a foreign language accompanied by a grant exemption from the local language requirement). Labeling bears the wording 'Exclusively for clinical investigations', is without CE marking, mentions manufacturer's and / or the EU-authorized representative's name / address / city (country), and warnings / precautions printed on the label are addressed in the risk analysis and v.v.

For the assessment of this technical documentation item it is assumed that the labeling of a non-market approved medical device should also comply with the Dutch language requirement for a CE-marked medical device. Labeling showed many major (13/19) and several minor (5/19) shortcomings. Labels with major shortcomings were not in Dutch and grant exemptions from the national language requirement were absent. In eight of these cases labeling did not comply with the essential requirements concerning the information to be supplied by the manufacturer. Labels with minor shortcomings were in Dutch; however, they did not comply with the essential requirements. Only one label was in Dutch *and* complied fully with the essential requirements.

Contents of Regulatory Files

Label (continued)

The wording ‘Exclusively for clinical investigations’, as explicitly required in the essential requirement 13.3.h of the MDD, was often not printed on the label (10/19). In two of these cases alternative wordings were used instead. Other shortcomings were related to the presence of CE marking (5/19), which is not allowed on an investigational device. In four of these cases labels included a CE mark with the identification number of the notified body. Additional shortcomings were related to the manufacturer’s and / or EU-authorized representative’s name / address / city (8/19):

- Manufacturer was not printed (n=1);
- Manufacturer’s address was not complete (n=6);
- EU-authorized representative was not printed (n=3);
- EU-authorized representative’s address was not complete (n=4).

The criterion concerning warnings / precautions is addressed in Section 3.4.4. Overall, the requirements for labeling were not addressed adequately.

Contents of Regulatory Files

Instructions for use

Good information for the user contains instructions for use in local language (or otherwise in a foreign language accompanied by a grant exemption from the local language requirement). Moreover, instructions for use comply with the essential requirements 13.6.a – 13.6.p. Instructions for use bear the wording 'Exclusively for clinical investigations', are without CE marking, mention manufacturer's and / or the EU-authorized representative's name / address / city (country), and warnings / precautions mentioned in the instructions for use are addressed in the risk analysis and v.v.

For the assessment of this particular technical documentation item it is assumed that instructions for use of a non-market approved medical device should also comply with the Dutch language requirement for a CE-marked medical device. Except for one, all instructions for use showed major shortcomings. In these eighteen cases the instructions for use were printed in English and grant exemptions from the national language requirement were absent. Furthermore, in twelve of these eighteen cases the instructions for use did not comply with the essential requirements concerning the information to be supplied by the manufacturer. Dutch instructions for use were only present in one case, which however did not comply with the essential requirements.

Contents of Regulatory Files

Post market surveillance procedure

A good post market surveillance procedure contains a procedure for the active collection and review of experiences, a description of resources to collect experiences other than customer-reported complaints, and a procedure for the lessons to be learnt from experiences such as a procedure for corrective and preventive actions taken, including updating the results of the risk analysis.

The assessment of the post market surveillance procedure was based on actual documentation as well as manufacturers' statements. A post market surveillance procedure is not required for non-market approved medical devices intended for clinical investigation in the current MDD, yet most manufacturers (13/19) submitted documentation. One manufacturer even submitted a surveillance procedure for non-market approved and CE-marked medical devices. Noticeably, in none of these technical documentation sets, the post market surveillance procedure was adequately addressed, mainly due to the absence of a proactive procedure to collect and review experiences, and the absence of a procedure for corrective and preventive actions including updating the risk analysis as an action to be taken. In two out of eleven cases, manufacturers submitted an unsubstantiated statement implying that a post market surveillance procedure was either maintained and not actually submitted, or under development and will be in place by commercial release. Four manufacturers stated that a post market surveillance procedure was not required for non-market approved medical devices and their corresponding item was rated accordingly.

Contents of Regulatory Files

Vigilance procedure

A good vigilance procedure contains a procedure for serious adverse event reporting mentioning the notification duty to competent authorities, and a procedure for the lessons to be learnt from serious adverse event reporting (changes in the product design, risk analysis, intended use, and labelling or instructions for use).

The principle of the vigilance procedure is to notify competent authorities of any malfunction or shortcoming that led to the death of a patient or user or led to a serious deterioration in the health of the subject that resulted in life threatening injury or illness. The vigilance procedure showed some major (5/19) and many minor shortcomings (13/19) due to the absence of a procedure for serious adverse event reporting (5/19), notification duty to competent authorities (5/19), and a procedure for corrective and preventive actions addressing the need to update the results of the risk analysis (17/19). Two manufacturers stated that the vigilance procedure was not required for non-market approved medical devices. Three manufacturers submitted an unsubstantiated statement that the vigilance procedure was maintained but was not actually submitted. Thus, in most cases the vigilance procedure was not adequately addressed.

Content

Conclusions

- For 95% of the manufacturers, the quality of a substantial part of the technical documentation explicitly required in the MDD was inadequate.
- The assessment revealed that 34% of the total number of all explicitly in the MDD required technical documentation items from all manufacturers had major shortcomings, 33% had minor shortcomings, and 34% had no shortcomings.
- Distributed over manufacturers, major shortcomings were found in nine out of ten types of assessed technical documentation items. Only the general description of the medical device showed merely minor shortcomings.

Conclusions

- Most major shortcomings were observed for the items concerning risk analysis, control and verification of the design, sterilization, labeling, instructions for use, and vigilance.
- In addition, the quality of technical documentation was inadequate for complementary items concerning medical devices incorporating a medicinal substance and post market surveillance.
- Although a post market surveillance procedure is not required for non-market approved medical devices in the current MDD, it is advisable that manufacturers indicate on how they practically implemented this issue. Actually, a clinical investigation is one of the first opportunities for manufacturers to collect and review experiences with medical devices in a proactive and systematic manner.
- Submitted technical documentation was often not well-structured.

Conclusions

- For European competent authorities and ethics committees, the outcome of the study could be a reason to consider the need for increased surveillance on medical devices intended for clinical investigation.
- The method described in this report provides a practical guide for manufacturers, notified bodies, competent authorities, and ethics committees to check whether technical documentation of medical devices contains the necessary aspects.

Content

Checklists

Availability check	*Absent*	*Present, final*	*Present, initial*	*NA*
1. General description of the MD	☐	☐	☐	
2. General description of any variants planned	☐	☐	☐	☐
3. Design specifications	☐	☐	☐	
4. Results of the risk analysis	☐	☐	☐	
5. List of applied standards	☐	☐	☐	☐
6. List of adopted solutions	☐	☐	☐	☐
7. Control and verification of the design	☐	☐	☐	
8. Proof of conformity when connected to other MD	☐	☐	☐	☐
9. Substance with ancillary action	☐	☐	☐	☐
10. Sterilisation	☐	☐	☐	☐
11. Label	☐	☐	☐	
12. Instructions for use	☐	☐	☐	☐
13. Post market surveillance procedure	☐	☐	☐	☐
14. Vigilance procedure	☐	☐	☐	
15. Statement of conformity assessment procedure	☐	☐	☐	

Note 2:

Checklists

General description of the MD

	Absent	Present
Name of the MD	☐	☐
Classification of the MD	☐	☐
Physical description	☐	☐
Drawing, diagram, and / or photograph	☐	☐
Mode of action	☐	☐
Intended use	☐	☐
Contraindications, warnings, precautions	☐	☐

Checklists

General description of any variants planned

	Absent	Present
NA		
Variants mentioned without physical description	☐	☐
Physical description of variants	☐	☐
Model numbers	☐	☐
Manufacturer’s statement: no variants are planned	☐	☐

Checklists

Design specifications

	Absent	Present	NA
(Design) drawings (if relevant)	□	□	
Specifications of materials used	□	□	
Product specifications	□	□	
Explanation for understanding drawings (if applicable)	□	□	

Checklists

Results of the risk analysis (RA)

	No	Yes
All foreseeable or known hazards are identified	☐	☐
Risks arising from identified hazards are estimated	☐	☐
Actions taken to reduce / eliminate risks are adequate	☐	☐
Residual risks are justified in relation to anticipated benefits	☐	☐

Checklists

List of applied standards

	No	Yes	NA
List of product standards corresponds	☐	☐	
Manufacturer's statement is present: standards N/A	☐	☐	☐
Product standards are N/A	☐	☐	☐

Checklists

List of adopted solutions if standards are not applied

	Absent	Present	NA
Checklist essential requirements including solutions	□	□	□
Separate list including solutions	□	□	□
Manufacturer’s statement: only standards are applied	□	□	□

Checklists

Control and verification of the design

	Absent	Present
Test results	☐	☐
Design verification techniques	☐	☐
Procedures	☐	☐
Manufacturer’s statement: QMS is maintained	☐	☐

Checklists

Proof of conformity if connected to other device

	Absent	Present	NA
Reference documentation in ER 9.1 or combination addressed in RA	☐	☐	☐
Description of actual combination	☐	☐	☐
Extensive proof of conformity	☐	☐	☐
Manufacturer’s statement: MD cannot be connected	☐	☐	☐

Checklists

Substance with ancillary action

	Absent	Present	NA
Intended purpose within the context of MD	□	□	□
Source and / or product license	□	□	□
Method of incorporation of substance into MD	□	□	□
Tests performed on substance	□	□	□
Procedure for pharmacovigilance	□	□	□
Notification duty for reporting serious adverse reaction to competent authority	□	□	□
Assessment of substance by national auth. / European Medicines Agency	□	□	□
Manufacturer’s statement: no substance with ancillary action used	□	□	□

Checklists

Sterilization

	Absent	Present	NA
Cleaning process (if applicable)	☐	☐	☐
Method of sterilization	☐	☐	☐
Parameters of sterilization process	☐	☐	☐
Summary of sterilization validation data	☐	☐	☐
Packaging material used	☐	☐	☐
Manufacturer’s statement: MD is non-sterile	☐	☐	☐

Checklists

Label

	No	Yes
Label in local language	☐	☐
Label complies with essential requirements	☐	☐

Additional information

Label bears wording ‘Exclusively for clinical investigations’	☐	☐
Label is without CE mark	☐	☐
Manufacturer’s / EU-authorized representative’s name / address / city is printed fully	☐	☐
Warnings / precautions on label are mentioned in RA	☐	☐

Checklists

Instructions for use (IFU)

	No	Yes	NA
IFU in local language	☐	☐	
IFU complies with essential requirements	☐	☐	
Manufacturer's statement: MD does not contain IFU	☐	☐	☐

Additional information

IFU bears wording 'Exclusively for clinical investigations'	☐	☐	
IFU is without CE mark	☐	☐	
Manufacturer's / EU-authorized representative's name / address / city is printed fully	☐	☐	
Warnings / precautions in IFU are mentioned in RA	☐	☐	

Checklists

Post market surveillance (PMS) procedure

	Absent	Present	NA
Manufacturer’s statement: PMS is maintained	☐	☐	☐
Complaint procedure for users	☐	☐	☐
Procedure for active collection / review of experiences	☐	☐	☐
Resource description	☐	☐	☐
CAPA procedure including RA update	☐	☐	☐
Manufacturer’s statement: PMS is not required	☐	☐	☐

Checklists

Vigilance procedure

	Absent	Present	NA
Manufacturer’s statement: vigilance is not required	☐	☐	☐
Manufacturer’s statement: vigilance is maintained	☐	☐	☐
Procedure for serious adverse event (SAE) reporting	☐	☐	
Notification duty for reporting SAE to competent authority	☐	☐	
Procedure for lessons to be learned, e.g. CAPA	☐	☐	

Checklists

Conformity assessment procedure

	Absent	Present
Manufacturer's statement; Conformity assessment procedure to be followed	□	□