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MedDev 2.7.1 Rev 4

**Medical Devices Regulation** 

## Clinical Evidence Requirements – Key Changes and Clarifications

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## Clinical Evidence Requirements

- 1. Frequency of updates to the Clinical Evaluation Report (CER)
- 2. Qualifications of report authors and evaluators
- 3. Specific and measurable objectives for the CER
- 4. Establishing the state of the art
- 5. Scientific validity of data
- 6. Equivalence
- 7. Access to data for equivalent devices
- 8. When is a clinical investigation required?
- 9. Risk-benefit
- 10. Post Market Surveillance (PMS) and Post Market Clinical Follow-up (PMCF)

- 1. Clause 6.2.3
- 2. Clause 6.4
- 3. Clause 7 + Appendix 5
- 4. Clause 8.2
- 5. Clause 9.3.1
  - Clause 8 + Appendix 5
  - Clause 9 + Appendix 6
  - Clause 10 + Appendix 7
- 6. Appendix 1
- 7. Appendix 12.2.3
- 8. Appendix 2
- 9. Appendix 7
- 10. Appendix 12

#### Clinical Evidence – MedDev 2.7.1 & MDR

# Clinical Evidence

- the clinical data and clinical evaluation report pertaining to a device
- sufficient amount and quality to allow a qualified assessment of whether the device achieves the intended clinical benefit(s) and safety, when used as intended by the manufacturer

# Clinical Evaluation

- a methodologically sound / systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device
- to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer

## Clinical Data

- clinical investigation on the device concerned
- clinical investigation reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated
- peer reviewed scientific literature on other clinical experience of either the device in question or a similar device for which equivalence can be demonstrated
- data from the manufacturer's post-market surveillance system, in particular post-market clinical follow-up



## MedDev 2.7.1 - 6.2.3 Updating the clinical evaluation

#### a. Frequency of updates

The manufacturer should define and justify the frequency at which the clinical evaluation needs to be actively updated. When doing so, the manufacturer should typically consider:

design changes or changes to manufacturing procedures (if any)

- risks, uncertainties or unanswered questions, in the medium or long term
- innovation, changes in clinical sciences, changes in materials sciences
- current confidence in the evaluation of clinical safety and performance (data available from clinical investigations, PMCF studies, registries, other systematic studies, total number of devices used in the market, expected reporting rates under the vigilance system)
- risks design, materials, components, invasiveness, clinical procedures, high-risk anatomical locations, high-risk populations, severity of disease, treatment challenges

## MedDev 2.7.1 - 6.2.3 Updating the clinical evaluation

The clinical evaluation is actively updated:

• on receipt of new information from PMS that has the potential to change the current evaluation

• at least annually if the device carries significant risks or is not yet well established

every 2 to 5 years if the device is not expected to carry significant risks and is well established

When involvement of notified bodies is required, updates are usually coordinated with the notified body. Typically, they are aligned with the timetable for surveillance audits and the renewal of the certificates.

## MDR – Article 60c – Periodic Safety Update Report

#### Article 60c – PSUR:

- Conclusions of the benefit risk determination
- Main findings of PMCF
- Volume of Sales
- Estimate of the Population that use the device
- Where practicable usage frequency of the device

- Manufacturers of class IIb and III devices shall update the report at least <u>annually</u>.
- Manufacturers of class IIa devices shall update the report when necessary and at least every two years.
- Manufacturers of devices in <u>class III</u> or <u>implantable</u> devices shall submit reports by means of the electronic system to the notified body.

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## MDR – Article 26 – Summary of Safety and Clinical Performance

#### Article 26 – SSCP:

- Manufacturer + SRN
- Device + UDI
- Intended Purpose, Indications, Contraindications
- Description, previous variant(s), differences, accessories, other products intended to be used in combination
- Possible diagnostic or therapeutic alternatives
- Harmonised Standards / Common Specifications
- Summary of the Clinical Evaluation Report + PMCF
- Suggested profile and training for users
- Information on residual risks, undesirable effects, warnings & precautions

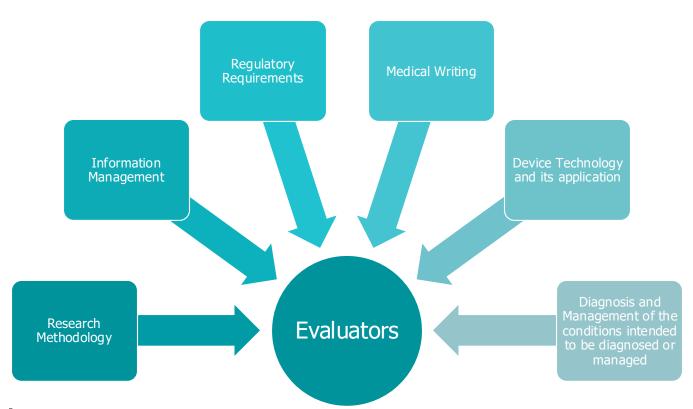
 In the case of devices classified as <u>class III</u> and <u>implantable devices</u>, the manufacturer shall draw up a summary of safety and clinical performance.

#### Article 49 – Clinical Evaluation

For devices classified as <u>class III</u> **and** <u>implantable devices</u>, the PMCF report and, if indicated, the summary of safety and clinical performance shall be <u>updated at least annually</u> with these data.

2. Qualifications of report authors and evaluators

#### MedDev 2.7.1 – 6.4 Who should perform the clinical evaluation?



Evaluators should have at least the following, in a relevant field:

- a degree from higher education in the respective field + 5 years of documented professional experience; or
- 10 years of documented professional experience if a degree is not a prerequisite for a given task.

There may be circumstances where expertise may be different; this should be documented and duly justified.



## MedDev 2.7.1 – 7 Definition of scope of the clinical evaluation

Device specification (technology, intended use, design history)



Essential Requirements requiring clinical evidence



Scope of clinical evaluation (products/models/sizes/settings, state of the art / benchmarks, conditions of and intended use, safety and performance requirements)



**Specific and measurable objectives** 

(Part of Clinical Evaluation Plan)

#### MedDev 2.7.1 – 7 Definition of scope of the clinical evaluation

- Depending on the stage in the lifecycle, considerations for setting up a clinical evaluation plan should include different aspects.
- Pre CE marking
- Post CE marking
  - No reliance on 'equivalence'
  - Need to benchmark / understand state of the art
  - Rely on data from the actual device

	Pre	Post
Device description	V	$\checkmark$
Design features, indications, target populations, specific claims	V	$\checkmark$
Equivalence	V	
Hazards, clinical risks	$\checkmark$	$\checkmark$
State of the art, standards, guidance, benchmark devices, medical alternatives	V	
Data sources	$\checkmark$	$\checkmark$
Design, material, manufacturing, information supplied changes		
Newly emerged clinical concerns		$\checkmark$
PMS – safety, performance, risks, benefits, claims		

## MedDev 2.7.1 – A5. Literature search and review protocol, key elements

# The literature search and literature review protocol (part of the Clinical Evaluation Plan) should:

- address the objectives of the review
- specify the methods for identification, selection, collection and appraisal of the relevant publications
- include the literature search methodology / protocol
- be objective, non-biased and systematic

#### **Examples are:**

- Cochrane Handbook for Systematic Reviews of Interventions
- PRISMA (The Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement
- MOOSE Proposal (Metaanalysis Of Observational Studies in Epidemiology)
- PICO (patient population, intervention, comparator / control, and outcome)

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## MedDev 2.7.1 – 7 Definition of scope of the clinical evaluation

Patients

Intervention

Control

Outcomes

- P: All intended patient populations, disease conditions, stage and severity of disease, etc?
- I: Adequately reflect intervention (ie, subject device or demonstrated equivalent device, duration, surgical technique)
- C: State of the art treatment options for conditions defined under P? Consider:
  - Choice of control (no treatment, drug, surgical intervention, other devices)
  - → Appropriateness and validation of benchmarks
- O: All claimed and implicit outcome measures associated with the device or treatment condition?

4. Establishing the state of the art

#### MedDev 2.7.1 – 8.2 Data retrieved from literature

State of the Art



#### State of the Art:

- applicable standards
- guidance documents
- data that relate to benchmark devices
- medical alternatives or to the specific medical conditions and patient populations intended to be managed with the device

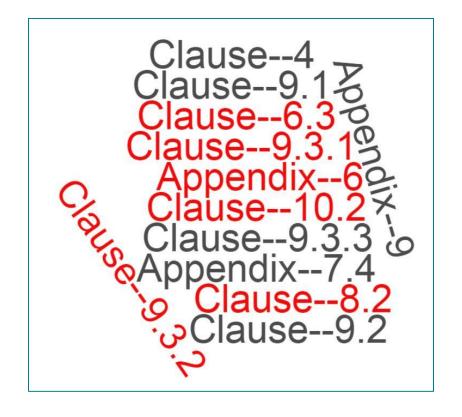
- The data are typically needed in order to:
  - identify the current knowledge in the corresponding medical field,
  - identify potential clinical hazards (due to substances, technologies, manufacturing procedures and impuries),
  - justify validity of criteria used for equivalence,
  - justify validity of endpoints.

5. Scientific validity of data

## MedDev 2.7.1 – 9.3.1. Evaluate methodological quality and scientific validity

- The evaluators should examine the methods used to generate / collect the data and evaluate the extent to which the safety or performance outcomes can be considered to be due to intervention with the device or due to:
  - confounding influences (natural course of the underlying medical condition, concomitant treatments)
  - bias
  - random error
  - inadequate disclosure of information
  - misinterpretation
- Some papers considered unsuitable for demonstration of adequate performance because of poor elements of the study design or inadequate analysis may still contain data suitable for safety analysis or vice versa.

**Sufficient clinical evidence:** an amount and quality of clinical evidence to guarantee the scientific validity of the conclusions





#### MedDev 2.7.1 Rev 3 / MedDev 2.7.1 Rev 4 / MDR – Equivalence

#### **Technical**

- be of similar design
- used under similar conditions of use
- have similar specifications and properties (e.g. physicochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength, software algorithms, porosity, particle size, nanotechnology, specific mass, atomic inclusions – nitrocarburising, oxidability)
- use similar deployment methods (if relevant)
- have similar principles of operation and critical performance requirements

#### **Biological**

- use same materials or substances in contact with the same human tissues or body fluids
- for a similar kind and duration of contact and similar release characteristics of substances
- including degradation products and leachables
- Exceptions can be foreseen for devices in contact with intact skin and minor components; in these cases risk analysis results may allow the use of similar materials taking into account the role and nature of the similar material. Evaluators should consider biological safety (e.g. ISO 10993) as well as other aspects necessary for a comprehensive demonstration of equivalence. A justification explaining the situation should be provided for any difference.

#### Clinical

- used for the same clinical condition or intended purpose (including similar severity and stage of disease, medical indication)
- at the same site in the body
- in a similar population (including age, gender, anatomy, physiology)
- have same kind of user
- not foreseen to deliver significantly different performances
- have similar relevant critical performance according to the expected clinical effect for a specific intended purpose

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#### MedDev 2.7.1 – A1 Demonstration of equivalence

#### For assuming equivalence:

- each device with which equivalence is claimed must fulfil all clinical, technical, biological characteristics;
- differences between the device under evaluation and the device presumed to be equivalent need to be identified, fully disclosed, and evaluated; explanations should be given why the differences are not expected to significantly affect the clinical safety and performance;
- potential impact of differences in manufacturing processes on technical and biological characteristics should be considered;
- where possible, clinically relevant specifications and properties should be measured both in the device under evaluation and the device presumed to be equivalent, and presented in comparative tabulations;
- comparative drawings or pictures should be included in order to compare shapes and sizes of elements that are in contact with the body;
- material characterisation and comparative testing in accordance with ISO 10993 series should be undertaken to demonstrate biological equivalence;
- data required to demonstrate equivalence should be summarised in the clinical evaluation, and the location of supporting information in the technical file cited.

#### MedDev 2.7.1 – A1 Demonstration of equivalence

#### For assuming equivalence:

- the manufacturer is expected to:
  - include supporting non-clinical information (e.g. pre-clinical study reports) in the technical documentation, and
  - in the clinical evaluation report, summarise the information and cite location in the technical documentation;
- for technical characteristics, devices that achieve the same therapeutic result by different means cannot be considered equivalent;
- for the evaluation of the biological characteristics:
  - for chemical characterisation of materials in contact with the body, ISO 10993-18 Annex C can be used for toxicological equivalence (this is just a part of the evaluation of the biological criteria);
  - sourcing and manufacturing procedures may adversely affect impurity profiles; analytical methods chosen to characterise medical devices should appropriately take into consideration knowledge concerning expected impurity profiles;
  - histopathological studies may be necessary to show that the same host response is achieved in vivo (intended application and intended duration of contact);
  - for animal tests, differences between species may limit predictive value; the choice of the test and predictive value should be justified;
  - abrasion, if relevant, and host response to particles may also need to be considered.



#### MedDev 2.7.1 – A1 Demonstration of equivalence

\*Similar means that no clinically significant difference in the performance and safety of the device would be due to differences;

Only clinical data obtained, when the equivalent device is a CE-marked medical device used in accordance with its intended purpose as documented in the IFU, are considered relevant.

Note: Exceptions can be considered.

When the equivalent device is <u>not a CE-marked device</u>, information concerning the regulatory status of the equivalent device and a justification for the use of its data should be included in the clinical evaluation report. The justification should <u>explain if the clinical data is transferrable to the European population</u>, and an <u>analysis of any gaps to good clinical practices</u> (such as ISO 14155) and <u>relevant harmonised standards</u>.

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7. Access to data for equivalent devices

## MedDev 2.7.1 — A12.2.3 — Clinical data from an equivalent device and other products

#### Equivalent devices

- The notified body should clearly document its assessment of clinical data presented from an equivalent device as part of a clinical evaluation. This should critically review and conclude on the equivalence or not of the device under assessment to the devices presented as equivalent in terms of their technical, biological and clinical characteristics. The relevance of each dataset from an equivalent device should be clearly evident and assessed by the notified body.
- The notified body should also <u>assess and document the level of</u> <u>access</u> to the technical and clinical data from an equivalent device that the manufacturer has.
- Relevant information may be commercially sensitive / confidential and not available to the manufacturer. The notified body should challenge the ability of the manufacturer to access information that are relevant to the demonstration of equivalence.
- Demonstration of equivalence might be difficult or impossible in case of limited access to the technical documentation of the devices.



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## MedDev 2.7.1 — A12.2.3 — Clinical data from an equivalent device and other products





- For hazard identification and when assessing the benefit/risk profile of the device, the notified body should consider current knowledge / the state of the art.
- The notified body should assess the appropriateness of the use of data from benchmark devices, other devices, and medical alternatives.



# MDR — Clinical Evaluation and Post-Market Clinical Follow-up — Annex XIII — Part A: Clinical Evaluation

- These characteristics shall <u>be similar to such an extent</u> that there would be <u>no clinically significant difference</u> in the clinical performance and safety of the device.
- Considerations of equivalence must always be based on proper scientific justification.
- Manufacturers must be able to clearly demonstrate that they have <u>sufficient levels of access</u> to the data on devices to which they are claiming equivalence in order to justify that claimed equivalence.





#### MDR – Clinical Evaluation and Investigation – Article 49 – Clinical Evaluation

- In the case of <u>implantable devices</u> <u>and</u> <u>devices falling within class III</u>, <u>clinical investigations shall</u> <u>be performed except if:</u>
  - the device has been designed by modifications of a device already marketed by the same manufacturer
  - the modified device has been demonstrated to be equivalent and this has been <u>endorsed</u> by the Notified Body (Annex XIII)

#### and

- the clinical evaluation is <u>sufficient</u> to demonstrate conformity with the relevant safety and performance requirements.
- In this case the notified body shall check that the PMCF plan is appropriate and includes post market studies to demonstrate the safety and performance of the device.
- Clinical investigations need <u>not</u> be performed in the following cases sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips or connectors for which the clinical evaluation is based on sufficient clinical data and is in compliance with the relevant product-specific common specification, where such a common specification is available

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... in view of similar well-established technologies – Delegated Act – add or remove to this list ...

#### MDR – Clinical Evaluation and Investigation – Article 49 – Clinical Evaluation

- A <u>manufacturer of a device demonstrated to be equivalent</u> to an already marketed device <u>not</u> <u>manufactured by him</u>, may not need to perform a clinical investigation provided that the following conditions are fulfilled in addition to what is required in the paragraph above:
  - the two manufacturers have a contract in place that explicitly allows the manufacturer of the second device full access to the technical documentation on an on going basis, and
  - the original clinical evaluation has been performed in compliance with the requirements of this Regulation,

#### and

the manufacturer of the second device provides clear evidence thereof to the notified body.

8. When is a clinical investigation required?

#### MedDev 2.7.1 – A2 When should clinical investigations be carried out?

#### How should manufacturers and evaluators decide if there is sufficient clinical evidence?

- When clinical data are required in order to draw conclusions as to the conformity of a device to the Essential Requirements, the data need to be in line with current knowledge / the state of the art, be scientifically sound, cover all aspects of the intended purpose and all products / models / sizes / settings foreseen by the manufacturer.
- If gaps are present that cannot be addressed by other means, clinical investigations should be planned and carried out.

Clinical Evaluation of Safety & Clinical Investigation on Device under Review

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## MedDev 2.7.1 – A2 When should clinical investigations be carried out?



#### **Devices likely to require clinical investigation data:**

- Implants / High-risk devices
- Devices based on technologies where there is little or no experience
- Devices that extend the intended purpose of an existing technology

#### **Annex X MDD / Annex 7 AIMDD:**

- Clinical investigations are required for implantable and class III devices unless it can be duly justified to rely on existing clinical data alone.
- The need for clinical investigations depends on the ability of the existing data to adequately address the safety, performance, benefit/risk profile, claims and side-effects in order to comply with the applicable Essential Requirements.
- Clinical investigations may also be required for other devices, including class
   I, class IIa and class IIb devices that are not implantable.



#### MedDev 2.7.1 – A2 When should clinical investigations be carried out?

#### **Special attention should be given to:**

- new design features, new materials,
- new intended purposes, new medical indications,
- new target populations (age, gender),
- new claims,
- new types of users (lay persons),
- seriousness of direct and/or indirect risks,
- contact with mucosal membranes or invasiveness,
- increasing duration of use or numbers of re-applications,
- incorporation of medicinal substances,
- use of animal tissues,
- medical alternatives with lower risks greater benefits are / become available,
- new risks are recognised (due to progress in medicine, science, technology),
- whether the data are amenable to evaluation through a clinical investigation





# MDR – Clinical Evaluation and Investigation – Article 49 – Clinical Evaluation (continued from slides #29 & #30)

- The requirement to perform clinical investigations shall not apply to implantable devices and devices falling into class III:
  - a) which have been lawfully placed on the market or put into service in accordance with Directive 90/385/EEC or Directive 93/42/EEC and for which the clinical evaluation
    - is based on sufficient clinical data and
    - is in compliance with the relevant product-specific common specification for the clinical evaluation of that kind of device, where such a common specification is available;

or















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and is in compliance with common specification for the clinical evaluation, if available

#### MDR – Clinical Evaluation and Investigation – Article 49 – Clinical Evaluation

- Except for <u>class III</u> and <u>implantable devices</u>, where demonstration of conformity with general safety and performance requirements <u>based on clinical data is not deemed appropriate</u>, adequate justification for any such exception shall be given based on the results of the manufacturer's risk management and on consideration of the specifics of the interaction between the device and the human body, the clinical performances intended and the claims of the manufacturer.
- The adequacy of demonstration of conformity with the general safety and performance requirements based on the results of non-clinical testing methods alone, including performance evaluation, bench testing and pre-clinical evaluation, has to be duly substantiated in the technical documentation referred to in Annex II.











## MedDev 2.7.1 – A7.2 Requirement for acceptable benefit/risk

- a) Evaluation of the description of the intended purpose of the device
- b) Evaluation of the device's benefits to the patient
- c) Quantification of benefit(s) to the patients
  - Probability of the patient experiencing one or more benefit(s)
  - Duration of effect(s)
- d) Evaluation of the clinical risks of devices (extent of risk(s) / harm(s), the following should be addressed individually and in aggregate):
  - Severity, number and rates of harmful events
  - Probability of a harmful event
  - Duration of harmful events
  - Risk from false-positive or false-negative results (diagnostic medical devices)
- e) Evaluation of acceptability of the benefit/risk profile









#### MedDev 2.7.1 – A12. Activities of notified bodies

# An audit as part of a quality system assessment, the notified body assesses:

- procedure clinical evaluation
- PMS plan
- PMCF plan
- results of PMCF

# A design or type examination dossier assessment, the notified body assesses:

- data presented in the clinical evaluation report
- validity of the conclusions drawn by the manufacturer
- conformity of the device to relevant essential requirements

#### In reviewing the evaluation of clinical data, the notified body verifies and concludes whether or not the manufacturer has adequately:

- provided detail of the PMS plan for the particular device and justified the appropriateness and adequacy of this plan
- clearly identified data needed from PMS and PMCF
- justified the appropriateness of the planned PMCF
- justified and documented if PMCF is not planned
- identified the sources of clinical data which will be gathered from the manufacturer's PMS system and PMCF



#### MDR – Technical Documentation on PMS – Annex IIa

## Information



## Plan



Proactive, systematic process to collect information to characterize, compare and assess the device

Clear, organized, readily searchable and unequivocal



Defines indicators & threshold values for risk benefit analysis

Defines complaint analysis methods including statistical analysis

Methods & protocols for trend reports
Procedures to identify, initiate & trace CAPA



Methods & protocols for CA, NB Economic Operator communication

Includes PMCF plan per Part B Annex XIII or justification if N/A

## Report

Class IIa, IIb & III Periodic safety Update Report article 60c

Class I Post Market Surveillance Report article 60ba

Technical
Documentation
Annex XIII Part B
PMCF evaluation
report

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## Questions & Answers

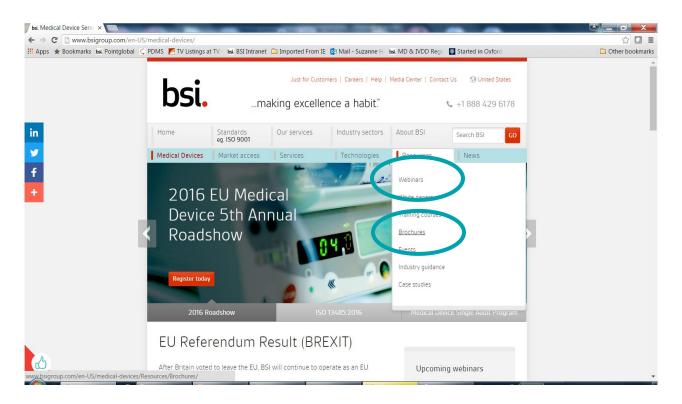
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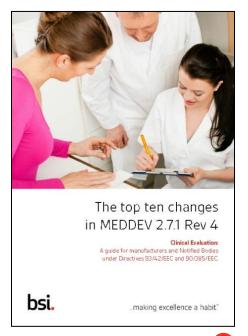


Brochure, Webinar & Whitepaper – MedDev 2.7.1 Rev 4 & MDR

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