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Clinical data and clinical evidence requirements

Approaching medical device clinical evaluations under MDR

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Acronyms

CDP: clinical development plan

CEP: clinical evaluation plan

CER: clinical evaluation report

CS: common specifications

DoA: Date of application

GSPR: General safety and performance requirements

MDD: Medical Device Directive (Council Directive 93/42/EEC amended by Directive 2007/47/EC)

MDR: Medical Device Regulation (Regulation (EU) 2017/745 amended by Regulation (EU) 2020/561)

PMS: post-market surveillance

PMCF: post-market clinical follow-up

QMS: quality management system

WET: well-established technology

1 Background

Clinical evaluation has always been a major critical activity for medical device manufacturers, with a significant impact on the R&D budget and on timing for obtaining the CE-mark. On the other side, for Notified Bodies and Regulatory Authorities, the amount and quality of clinical data has always been a highly debated topic with medical devices' manufactures.
Provisions related to clinical data were already part of Directive 93/42/EEC on medical devices, adopted in 1993. This specified that requirements concerning device safety and performance were to be based on clinical data; the need to critically evaluate those data was referred to as "clinical evaluation", to which Annex X was devoted.

In 2003 the European Commission published its first guideline on clinical evaluation - MEDDEV 2.7/1 - intending to provide guidance to manufacturers on analyzing and reviewing clinical data, and to Notified Bodies when reviewing the clinical evaluation as part of the conformity assessment procedure.

In 2007, Directive 93/42/EEC was amended by Directive 2007/47/EC, which included the implementation of provisions regarding clinical data: it was noted that often manufacturers still did not have clinical data available, so that Notified Bodies were not always able to verify the adequacy of data provided sufficiently. Directive 2007/47/EC clarified that clinical data were generally required for all medical devices - regardless of their classification - and introduced the definition of "clinical data" (Art. 1(2)(k)).

On 26 May 2017, the Medical Device Regulation (EU) 2017/745 repealing Directive 93/42/EEC entered into force. The Medical Device Regulation provides greater detail and additional requirements concerning the process of clinical evaluation, for compliance with relevant general safety and performance requirements.
The latest version of MEDDEV 2.7/1 (rev. 4), issued in June 2016, was written with respect to the Directive; therefore, it is not fully aligned with the new Regulation, which represents the current authentic law. Thus, it is important that non-harmonized aspects are taken into account when planning and conducting a clinical evaluation under the Medical Device Regulation.
This guidance is intended to help you understand new provisions regarding clinical data and their critical evaluation, and to clarify what sufficient clinical evidence means under Regulation (EU) 2017/745.

2 Introduction

The entry into force of Regulation (EU) 2017/745 (hereinafter also referred to as "MDR") established a new regulatory framework, primarily aimed at ensuring the smooth functioning of the medical device market and a high level of protection of health for patients and users, setting higher standards of quality and safety for medical devices.
The date of application (DoA) of the MDR was intended to be 26 May 2020, 3 years after it entered into force.

Recently, the COVID-19 outbreak and the associated public health crisis has forced the medical device industry to face unprecedented challenges, that were impossible to anticipate at the time of the MDR adoption. These challenges constitute an immense burden for all parties involved, including economic operators, national authorities, health institutions, and citizens. The crisis we are living in has created extraordinary circumstances, demanding substantial additional resources and increased availability of vitally important devices.
Given these challenges and taking into account the complexity of the MDR and its requirements, in April 2020 the European Parliament and Council accepted the proposal of the Commission to postpone the DoA of the MDR by one year, by means of Regulation (EU) 2020/561. This was based on the fact that it was very unlikely that the Member States, health institutions, and economic operators, would have been in a position to ensure the proper implementation and application of the MDR requirements from May 2020.

In this context, MDR Art. 120 is particularly relevant. It provides time limits on how long devices with valid CE certificates obtained under the old Directive (the so-called "legacy devices") can be placed on the market or put into service after the MDR DoA. What is particularly important for this expert guidance is that the amendment of the Art. 120 extends the timeframe for manufacturers to align with the MDR requirements regarding post-market surveillance (PMS) activities and, in this context, post-market clinical follow-up (PMCF); new PMS and PMCF provisions will apply from 26 May 2021 in place of the previous requirement of application from 26 May 2020.

3 Scope

This expert guidance will help you understand the MDR requirements for clinical data and clinical evidence, and to clarify major gaps between the old Directive (hereinafter also referred to as "MDD"), MDR and the current MEDDEV 2.7/1 guideline.

Main topics addressed in this document are:

- **The update of the "clinical data" definition by MDR,**
- **The new definition for "clinical evidence",**
- **The new definition for "clinical evaluation",**
- **The practicability of the equivalence route under the MDR,**
- **The requirements for an MDR-compliant clinical evaluation, especially concerning legacy devices,**
- **The requirements for clinical data of medical devices without an intended medical purpose (MDR Annex XVI),**
- **The use of clinical data of similar medical devices,**
- **The MDR requirements for PMCF, in the context of PMS activities.**

4 The concept of "clinical data", "clinical evidence" and "clinical evaluation": new requirements under MDR

As mentioned in the Section 1 of this guidance, clinical data definition was already provided by MDD. MEDDEV 2.7/1:2016 provides itself a definition of clinical data, as well as the IMDRF[1] guidelines recently issued, concerning clinical evidence and clinical evaluation applicable to medical devices (IMDRF MDCE WG/N55 and N56).

To help ensure a clear understanding of MDR requirements related to clinical data, it is essential to take note of the MDR definition of "clinical data" and its related terms, namely "clinical evidence" and "clinical evaluation".

Definitions are provided in Table 1 below. Similarities and differences, especially between MDD and MDR, are also highlighted

Table 1. Comparison of definitions in the MDD, MEDDEV 2.7/1:2016, MDR, and IMDRF N55 guideline on clinical evidence.

Term	Dir. 93/42/EEC amended by Dir. 2007/47/EC (MDD)	MEDDEV 2.7/1:2016 rev.4	IMDRF MDCE WG/N55 FINAL:2019	Reg. (EU) 2017/745 amended by Reg. (EU) 2020/561 (MDR)
Clinical data	Art. 1(2)(k): Clinical data means the safety and/or performance information that is generated from the use of a device. Clinical data are sourced from: - clinical investigation(s) of the device concerned, or - clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated, or - **published and/or unpublished reports on other clinical experience** of either the device in question or a similar device for which equivalence to the device in question can be demonstrated.	Paragraph 4 ("Definitions"): Clinical data: the safety and/or performance information that is generated from the clinical use of a device. Clinical data are sourced from: - clinical investigation(s) of the device concerned; or - clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated; or - published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated. Note(s): definition derived from Article 1(2)(k) of MDD.	Paragraph 4 ("Definitions and Concepts", 4.2 ("Clinical data")): Definition: safety, clinical performance and/or effectiveness information that is generated from the clinical use of a medical device. Explanation: sources of clinical data may include: (i) results of pre- and post-market clinical investigation(s) of the device concerned, (ii) results of pre- and post-market clinical investigation(s) or other studies reported in the scientific literature of a comparable device; (iii) published and/or unpublished reports on clinical experience of either the device in question or a comparable device, (iv) other sources of clinical experience such as registries, adverse event databases, and medical records. Note(s): IMDRF guideline on clinical evaluation (N56) provides the same "clinical data" definition, but without reporting the Explanation of N55 guideline.	Art. 2(48): Clinical data means information concerning the safety or performance that is generated from the use of a device and is sourced from the following: - clinical investigation(s) of the device concerned, - clinical investigation(s) or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated, - **reports published in peer reviewed scientific literature on other clinical experience** of either the device in question or a device for which equivalence to the device in question can be demonstrated, - clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up.

Comments: The definition of MEDDEV 2.7/1 is analogous to that provided by MDD, allowing both published and unpublished reports on other clinical experience to contribute to the clinical evaluation. This definition is also similar to what is reported in IMDRF N55 guidance of October 2019.
It is observed that MDD and MEDDEV 2.7/1 are not fully aligned with the MDR, providing a narrower definition of what constitutes clinical data. The MDR specifies that clinical data contributing to the clinical evaluation of medical devices is represented by data coming from clinical investigations on the device concerned and/or on an equivalent device, clinically relevant information coming from PMS and in particular PMCF, and reports published in peer reviewed scientific literature on other clinical experience both gained on the device concerned and on an equivalent device.

[1] International Medical Device Regulators Forum (IMDRF), previously known as the Global Harmonization Task Force on Medical Devices (GHTF).

Term	Dir. 93/42/EEC amended by Dir. 2007/47/EC (MDD)	MEDDEV 2.7/1:2016 rev.4	IMDRF MDCE WG/N55 FINAL:2019	Reg. (EU) 2017/745 amended by Reg. (EU) 2020/561 (MDR)
Clinical evidence	Not defined	Paragraph 4: Clinical evidence: the clinical data and the clinical evaluation report pertaining to a medical device. Note(s): Definition adopted from GHTF SG5/N2R8:2007.	Paragraph 4 ("Definitions and Concepts", 4.4 ("Clinical evidence")): Definition: The clinical data and its evaluation pertaining to a medical device. Explanation: Clinical evidence is an important component of the technical documentation of a medical device, which along with other design verification and validation documentation, device description, labelling, risk analysis and manufacturing information, is needed to allow a manufacturer to demonstrate conformity with the Essential Principles. It should be cross-referenced to other relevant parts of the technical documentation that impact on its interpretation. In accordance with applicable local regulations, clinical evidence, in part or in total, may be submitted to and reviewed by conformity assessment bodies and regulatory authorities. The clinical evidence is used to support the marketing of the medical device, including any claims made about the safety, clinical performance and/or effectiveness of the device, and the labelling of the device. Clinical evidence should be reviewed and updated throughout the product life cycle by the manufacturer as new information relating to safety, clinical performance and/or effectiveness is obtained from clinical experience during marketing of the device in question and/or comparable devices.	Article 2(51): Clinical data and clinical evaluation results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer.

Comments: A definition for "clinical evidence" is not provided by MDD, but is provided by MEDDEV 2.7/1, IMDRF N55 and MDR. IMDRF N55 guidance defines "clinical evidence" as the evaluation of clinical data pertaining to a medical device, and introduces the concept of clinical data review and update throughout the life cycle of a medical device.
The definition of "clinical evidence" provided by the MDR is more prescriptive, and specifies that to qualify as clinical evidence, the clinical data and clinical evaluation report must be of sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves its intended clinical benefit(s), when used as intended by the manufacturer. To that end, manufacturers shall plan and conduct a clinical evaluation in accordance with Article 61 and Part A of Annex XIV.

The diversity of medical devices and the technologies on which they are based pose unique challenges for manufacturers, conformity assessment bodies, and regulators when trying to identify what should constitute evidence sufficient to demonstrate compliance with the general safety and performance requirements (GSPR).

Some technologies have been available for many years and are well characterized from a safety, clinical performance and/or effectiveness viewpoint. On the other hand, many devices utilize new, state-of-the-art technology that has had little prior application. Furthermore, their intended purpose and clinical application can vary widely, with end results influenced by a wide range of different and differently experienced end-users. Given the complexity of the medical devices milieu, the assessment of what is acceptable clinical evidence must be undertaken on a case-by-case basis.

Term	Dir. 93/42/EEC amended by Dir. 2007/47/EC (MDD)	MEDDEV 2.7/1:2016 rev.4	IMDRF MDCE WG/N55 FINAL:2019	Reg. (EU) 2017/745 amended by Reg. (EU) 2020/561 (MDR)
Clinical evaluation	Not defined	Paragraph 4: Clinical evaluation: a methodologically sound ongoing procedure to collect, appraise and analyse clinical data pertaining to a medical device and to evaluate whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer's Instructions for Use.	Paragraph 4 ("Definitions"): A set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety, clinical performance and/or effectiveness of the device when used as intended by the manufacturer. Note(s): the same definition is provided by IMDRF MDCE WG/N55 FINAL:2019 on clinical evidence.	Article 2(44): Clinical evaluation means a systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer.

Comments: A definition for "clinical evaluation" is not present in the MDD, but is provided by MEDDEV 2.7/1, IMDRF N55, IMDRF N56, and MDR. The MDR definition is more stringent than the definition of MEDDEV 2.7/1 and IMDRF, because it:
• Uses the word "continuously" when describing the activities to be carried out for clinical evaluation, indirectly referring to the definition of PMCF. While the term "continuously" is similar to the word "ongoing", it has a slightly more active connotation;
• Specifies that the purpose of the clinical evaluation is to verify the safety, performance, and benefits of the device. The requirement that clinical evaluation verifies compliance is very similar to the purpose of clinical evaluation as stated in the MEDDEV 2.7/1, but is more direct;
• Includes the specific requirement that the clinical evaluation verifies not only safety and performance, but also clinical benefits[2]; the need to consider clinical benefits is a crucial recurrent theme in the MDR, also present in the definition of clinical evidence.

Take-home messages

In accordance with the MDR, unpublished reports on other clinical experience on the device subject of the evaluation and/or on an equivalent device do not constitute clinical data, meaning that they cannot contribute to the clinical evaluation of medical devices.

In accordance with the MDR, clinical evidence must be of sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves its intended clinical benefits. To that end, manufacturers shall plan, conduct and document a clinical evaluation.

The clinical evaluation shall be planned, and the plan shall be designed on a case-by-case basis, due to the wide variety of device types and technologies constituting the medical devices milieu.

The MDR specifies that the clinical evaluation is a "continuous" process, so it has to be updated during the entire life cycle of a medical device, reinforcing MDD provisions on PMCF.

The MDR stresses the concept of "clinical benefit", meaning the impact of a device on the health of an individual. Clinical benefits shall be distinguished from clinical performances, but both shall be verified by means of the clinical evaluation.

[2] MDR Article 2(53) states that clinical benefit "means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health".

5 Requirements for clinical evaluation under MDR

The MDR reinforces several important factors relevant to the clinical evaluation, and especially:

1. the consideration of available alternative treatment options in the context of a medical device's clinical evaluation;
2. the definition of equivalence and the process to demonstrate equivalence, which are included in the text of the MDR;
3. the incorporation of PMS data and PMCF into the process of clinical evaluation.

5.1 Current knowledge and state of the art

MDR Annex I on GSPR states that medical devices shall be safe and effective and shall not compromise the clinical condition or safety of patients/users/other persons, provided that:

- all risks which may be associated with those devices are acceptable when weighed against benefits, and
- devices are compatible with a high level of protection of health and safety.

This has to be established by taking into account the generally acknowledged state of the art.

This concept is definitely not new: as reported by MEDDEV 2.7/1 rev.4, the current knowledge/state of the art in the corresponding medical field shall be part of the clinical evaluation of medical devices; it has to be updated through their life cycle, and mainly includes:

- applicable standards and guidance documents,
- information relating to the medical condition managed with the device and its natural course,
- benchmark devices and medical alternatives available to the target population.

When preparing a clinical evaluation, whether in accordance with MDD or MDR, it is important that these aspects are taken into account, and that a thorough and comprehensive literature search is conducted. In this regard, par. 8.2 of MEDDEV 2.7/1 specifies that the literature search shall be carried out based on a protocol, documenting the planning of the search before execution. It is important that the search is documented to such a degree that it can be reproduced, if necessary. In our experience, what is often unconsidered or underestimated is that these considerations are valid also for the state of the art literature search, aside from the search of clinical data pertaining to the device under evaluation and/or its equivalent.

Take-home messages

- **in accordance with the MDR, the clinical evaluation has to consider available alternative treatment options in the relevant medical field, taking into account the clinical indications of the device concerned;**
- **literature search pertaining to the current knowledge/state of art shall be based on a protocol and its results shall be documented, in order to ensure that the process is traceable and reproducible.**

5.2 Equivalence route in accordance with MDR

As discussed in par. 4 of this guidance, data on a medical device for which equivalence to the device under evaluation has been demonstrated, may represent one of the clinical data sources under MDR.

When demonstrating equivalence to another device, the MDR requires that technical, biological and clinical characteristics are considered. While these general characteristics are also described in MEDDEV 2.7/1 rev. 4, and are aligned with the MDR requirements, there are differences in the criteria that are set out for each of the three characteristics. For the purpose of clarification, differences between MDR, MDD, and MEDDEV 2.7/1 are highlighted in Table 2.

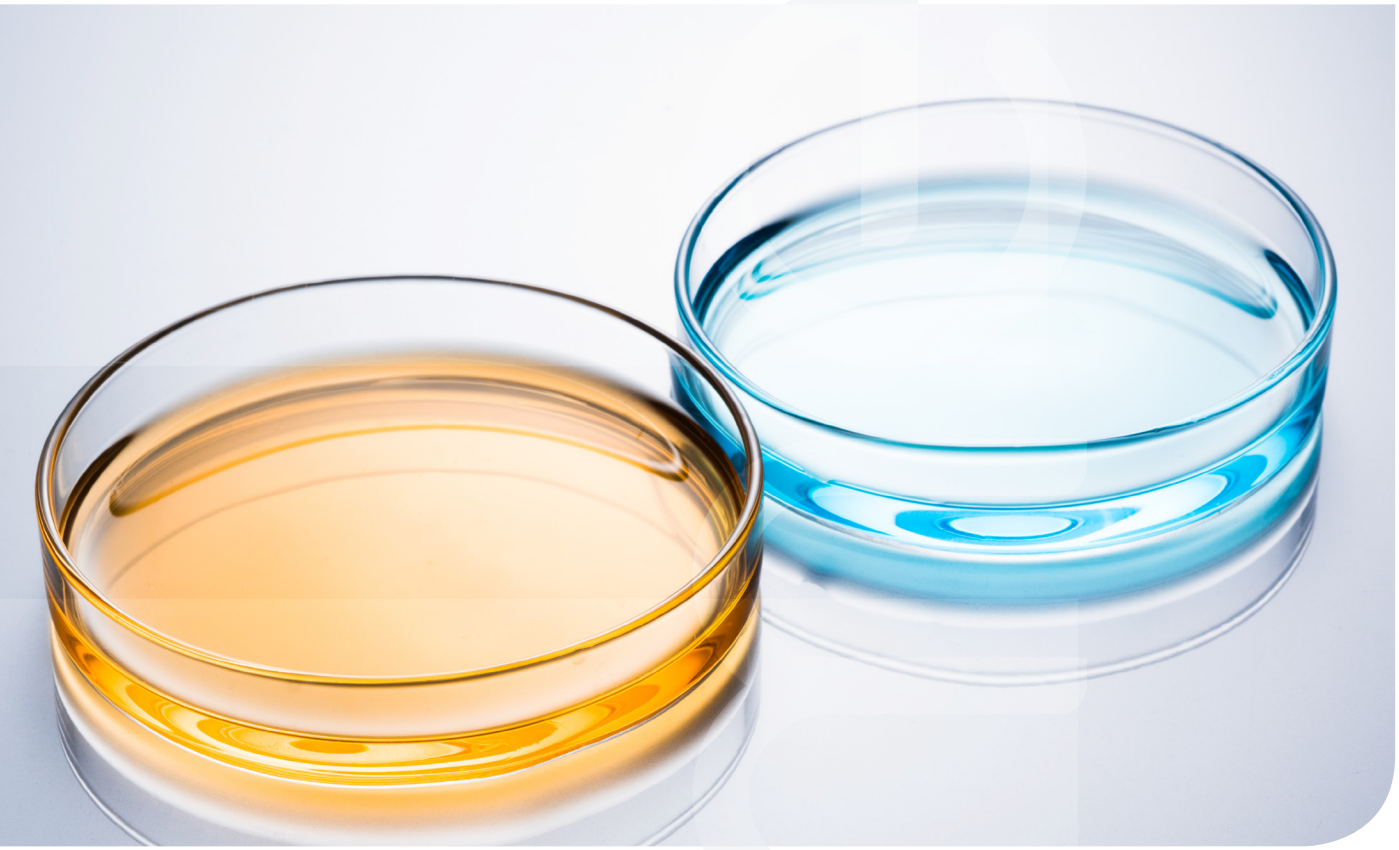


Table 2. Equivalence characteristics and criteria: differences between MDR, MDD and MEDDEV 2.7/1:2016.

Equivalence	Dir. 93/42/EEC amended by Dir. 2007/47/EC (MDD)	IMDRF MDCE WG/N55 FINAL:2019	Reg. (EU) 2017/745 amended by Reg. (EU) 2020/561 (MDR)
Technical	Not defined	- be of similar design, and - **used under the same conditions of use,** and - have similar specifications and properties (e.g. physicochemical properties such as type and intensity of energy, tensile strength, viscosity, surface characteristics, wavelength, surface texture, porosity, particle size, nanotechnology, specific mass, atomic inclusions such as nitrocarburising, oxidability), and - use similar deployment methods (if relevant), and - have similar principles of operation and critical performance requirements.	The device is of similar design; is used **under similar conditions of use**; has similar specifications and properties including physicochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength and **software algorithms;** uses similar deployment methods, where relevant; has similar principles of operation and critical performance requirements.

Comments: Under the MDR, conditions for use shall be similar to the extent that there would be no clinically significant differences in devices' performance and safety.

Equivalence	Dir. 93/42/EEC amended by Dir. 2007/47/EC (MDD)	IMDRF MDCE WG/N55 FINAL:2019	Reg. (EU) 2017/745 amended by Reg. (EU) 2020/561 (MDR)
Biological	Not defined	Use the same materials or substances in contact with the same human tissues or body fluids. **Exceptions** can be foreseen for devices in contact with intact skin and minor components of devices; in these cases, risk analysis results may allow the use of similar materials taking into account the role and nature of the similar material.	The device uses the 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.**

Comments: The exceptions outlined in MEDDEV 2.7/1 regarding the use of different materials are no longer acceptable under the MDR. For biological equivalence demonstration, the principles outlined in the ISO 10993 series of standards for the biological evaluation of medical devices can be adopted: ISO 10993-1 describes a risk-based approach for biological evaluation and ISO 10993-18 can be used for chemical characterization of materials, in order to specify the identity of materials and to estimate the type and quantity of leachables from the final medical device.

The MDR has additional requirements for devices that are composed of substances or combinations of substances that are intended to be introduced into the human body, and that are absorbed by or locally dispersed in the human body. For the consideration of equivalence, the substances shall be the same. For their conformity assessment under MDR, those devices shall comply with the relevant requirements laid down in Annex I to Directive 2001/83/EC on medicinal products for human use with regard to the evaluation of absorption, distribution, metabolism, and excretion (ADME), but also local tolerance, toxicity, interaction with other devices/medicinal products/other substances and potential for adverse reactions. For the demonstration of equivalence under the MDR, these aspects shall be taken into consideration.

With reference to medical devices containing an ancillary medicinal substance (class III under Rule 14), MDCG 2020-53 guideline specifies that equivalence cannot be claimed to a device without an ancillary medicinal substance and vice versa. Similarly, manufacturers shall not claim equivalence of the ancillary medicinal substance to a "standalone" medicinal substance.

Equivalence	Dir. 93/42/EEC amended by Dir. 2007/47/EC (MDD)	IMDRF MDCE WG/N55 FINAL:2019	Reg. (EU) 2017/745 amended by Reg. (EU) 2020/561 (MDR)
Clinical	Not defined	- used for the same clinical condition (including when applicable similar severity and stage of disease, **same medical indication**), and - used for the same intended purpose, and - used at the same site in the body, and - used in a similar population (this may relate to age, **gender**, anatomy, physiology, possibly other aspects), and - not foreseen to deliver significantly different performances (in the relevant critical performances such as the expected clinical effect, the specific intended purpose, the **duration of use**, etc.).	The device is used for the **same clinical condition or purpos**e, including similar severity and stage of disease, at the same site in the body, in a similar population, including as regards age, anatomy and physiology; has **the same kind of user**; has similar relevant critical performance in view of the expected clinical effect for a specific intended purpose.

Comments: Under the MDR, when considering equivalence between the device under evaluation and the presumed equivalent device, manufacturers shall take into account whether the intended user's competence or knowledge can have any impact on safety, clinical performance and outcome.

In accordance with Annex XIV, Part A (3) of the MDR, considerations of equivalence shall be based on proper scientific justification.
Furthermore, it shall be clearly demonstrated that manufacturers have sufficient levels of access to the data relating to the device with which they are claiming equivalence. This implies that technical, biological and clinical characteristics shall be duly investigated and documented, and any difference between the two devices is disclosed.
If a manufacturer cannot demonstrate sufficient levels of access to the data relating to the presumed equivalent device, then equivalence cannot be claimed for the purpose of conformity assessment.

[3] MDCG 2020-5 published in April 2020 provides guidance on the equivalence demonstration in the context of medical device clinical evaluation.

• Specific requirements for class III and implantable medical devices

In accordance with MDR Art. 61(4), manufacturers of implantable or class III medical devices, including devices containing an ancillary medicinal substance, shall perform clinical investigations, but exceptions are provided.

Clinical investigations do not necessarily need to be conducted if:

- the device has been designed by modifications of a device already marketed by the same manufacturer,
- equivalence can be demonstrated according to the MDR, and
- the clinical evaluation of the marketed device is sufficient to demonstrate conformity with the relevant safety and performance requirements

A marketed device is considered to be a device already placed on the market, CE-marked with respect to the old Directives or the MDR, with a valid CE marking, an updated clinical evaluation, and with a favourable benefit-risk ratio.

For implantable and class III devices claiming equivalence to an already marketed device not manufactured by the same company, in addition to the above requirements, the manufacturer must have a contract in place to allow full access to the technical and clinical documentation of the equivalent device on an ongoing basis (Art. 61(5)). In this case, it is also required that the original clinical evaluation of the equivalent device has been performed in compliance with MDR requirements. MDCG 2020-5 clarifies that this implies that the presumed equivalent device is certified under the MDR: in case the equivalent device is not marketed by the same company, it will not be possible to claim equivalence if that device is certified with respect to the MDD.

According to Article 61(6), the requirement to perform clinical investigations pursuant to par. 4 shall not apply to implantable and class III devices:

a) which are legacy devices, and for which the clinical evaluation:

- is based on sufficient clinical data, and
- is in compliance with the relevant Common Specifications (CS) for the clinical evaluation of that kind of device (if applicable/available)

b) that are 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 CS, if available.

• Requirements for medical devices different from class III and implantable products

For devices other than implantable and class III devices, MDR Article 61(3) is applicable. This requirement does not specify whether the device is presumed to be marketed within the EU. Therefore, it will be possible to claim equivalence to a device certified both with respect to MDD or MDR, but also to a device that is not CE-marked, provided all relevant MDR requirements regarding equivalence and clinical evaluation are met. These include:

- that the manufacturer has sufficient levels of access to the data relating to the device with which equivalence is claimed;
- that clinical investigations were conducted in accordance with international guidelines for good clinical practices;
- that the clinical data meet the requirements of the MDR, and a justification is provided whether these are transferrable to the European population.

In the circumstance that the presumed equivalent device is from another company, there is no requirement of a contract between the manufacturers for regulating the access to the technical documentation.

MEDDEV 2.7/1 already specifies that clinical data pertaining to a non CE-marked medical device could be used for clinical evaluation; in this case, information concerning the regulatory status of the product deemed to be equivalent - and a justification for the use of its data - should be included in the clinical evaluation report (CER). The justification should not only explain if the clinical data are transferrable to the European population, but also analyze any gaps to good clinical practices (ISO 14155) and relevant harmonized standards.

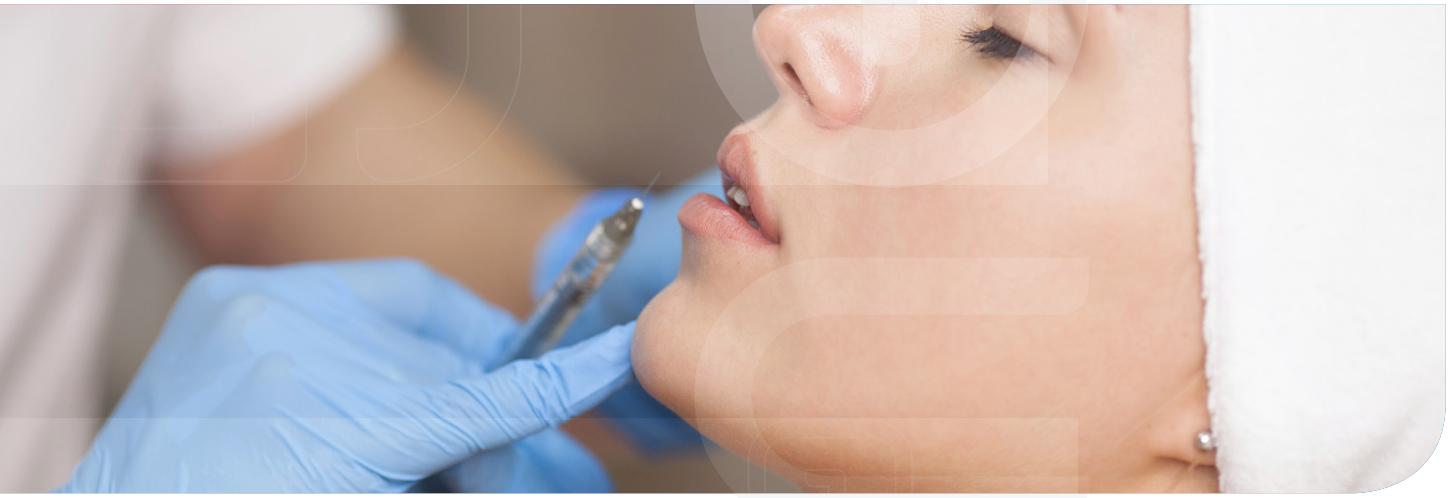
Take-home messages

- **For implantable and class III devices, when equivalence is claimed to a device derived from modifications of an "originator" marketed by the same company, the originator can be CE-marked under either the old Directives or the MDR.**
- **For implantable and class III devices, when equivalence is claimed to a device marketed by another manufacturer, a contract has to be in place to allow the manufacturer of the device under evaluation to access the technical documentation of the second device.**
- **For devices other than class III and implantable, equivalence could be claimed for a device CE-marked under MDD or MDR. In this case, the MDR does not explicitly require a contract to be in place between the manufacturer and the company of the device for which equivalence is claimed. Equivalence could also be claimed for medical devices that are not CE-marked and marketed within the EU, provided that MDR provisions for clinical evaluation are met.**
- **In any case, and regardless of the need to formally have a contract in place with the manufacturer of the equivalent device, the manufacturer shall demonstrate access on an ongoing basis to the equivalent device documentation.**

6 Clinical evaluation for medical devices without a medical purpose: the concept of an analogous device

The MDR covers certain groups of products without an intended medical purpose as medical devices, such as those listed in Annex XVI.
The MDR states that clinical investigations shall be performed for these devices, unless reliance on clinical data from an analogous medical device is duly justified (Art. 61(9)).
An analogous medical device is understood as a device which:

- Is similar in terms of functioning,
- Is similar in terms of risk profile, and
- Has a medical purpose



To justify reliance on clinical data from an analogous device, the demonstration of equivalence should be conducted with the acceptance that the device under evaluation will only have a non-medical purpose whereas the analogous device has a medical purpose. Also, the general requirement to demonstrate a clinical benefit shall be understood as a requirement to demonstrate the performance of the device.
Since CS for the products without an intended medical purpose may have requirements related to the clinical evaluation specifically regarding safety, these will have to be taken into consideration when demonstrating equivalence.

If a device has a medical and non-medical purpose, it should fulfill the requirements for devices with, as well as without an intended medical purpose, in accordance with MDR recital 12.

For devices without an intended medical purpose, the clinical evaluation could rely on existing data from an "analogous device". Otherwise, clinical investigations shall be performed. The analogous device shall be similar in terms of functioning and risk profile, but shall have a medical purpose.

7 Use of clinical data from similar devices

As suggested by MDCG 2020-5 guidance, the term "similar devices" may be understood as devices belonging to the same generic group. The MDR defines "generic device group" in Article 2(7) as a set of devices having the same or similar intended purposes or a commonality of technology allowing them to be classified in a generic manner, not reflecting specific characteristics.

Data from similar devices can be considered during the clinical evaluation process, as these serve an indirect supportive role. Data that are not pivotal, thus not directly demonstrating the safety and clinical performance of the device concerned, can be included in the clinical evaluation for a variety of purposes, as also reported by MEDDEV 2.7/1 rev.4:

- Identifying and defining the state of the art and alternative treatment options in the corresponding medical field,
- Ensuring that the risk management process, and thus the Risk Management File, are comprehensive, by identifying relevant hazards, hazardous situations and associated clinical risks, and by identifying acceptable occurrence rates of risks and adverse events,
- Helping to define the scope of the clinical evaluation, by identifying any design features in similar devices that pose special performance or safety concerns,
- Identifying relevant and specified clinical outcome parameters for the intended clinical benefits, and defining minimum requirements for a quantified clinical benefit that is considered clinically relevant,
- Providing input for designing pre- and post-market clinical investigations (pivotal studies).

7.1 Clinical evaluation for well-established technology devices

"Well-established technology" (WET) is a terminology used in Article 52(5) and Article 61(8) of the MDR, but a definition is not actually provided. It is in MDCG 2020-6[4] guidance that it is clarified that devices belonging to WET have the following common features:

- They are characterized by relatively simple, common and stable designs, with little evolution;
- Their generic device group has well-known safety and has not been associated with safety issues in the past;
- They have well-known clinical performance characteristics;
- Their generic device group is composed by standard of care devices where there is little evolution in indications and the state of the art;
- They are characterized by a long history on the market.

[4] MDCG 2020-6 guidance issued in April 2020 concerns to clinical evidence needed under MDR for medical devices previously CE-marked under Dir. 93/42/EEC or Dir. 90/385/EC.

As previously reported in this expert guidance, in accordance with MDR Art. 61(6b), the requirement to perform clinical investigations shall not apply to implantable and class III devices belonging to a specific subset of WET: sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, etc., and for which the clinical evaluation is based on sufficient clinical data and is in compliance with the CS, if available.

The basic clinical evaluation requirements for legacy devices described in Article 61(6a) and the devices of Article 61(6b) are the same: "sufficient clinical data" and compliance to CS. The distinction between the two is that the WET of Article 61(6b) are not explicitly required to have had prior certification under the old Directives to be exempted from the requirement for clinical investigations that otherwise apply to class III and implantable devices.

As reported by MDR Annex XIV, for devices identifiable as WET the clinical evaluation can be based on data coming from similar devices. For low risk standard of care devices where there is little evolution in state of the art, a lower level of clinical evidence may be justified. In these cases, the clinical evaluation may be supported by clinical data coming from PMS activities, provided that there has been a quality management system (QMS) in place to systematically collect relevant post-market data, and that these actually support the safety, performance and the benefit-risk profile of the device.

Take-home messages

- **Data pertaining to similar devices belonging to the same generic device group can be considered and included in the clinical evaluation of a medical device, but generally it would serve only the role of indirect supportive data (non-pivotal).**
- **For a specific subset of WET, as those described in Article 61(6b), clinical investigations are not deemed to be necessary if the clinical evaluation is based on sufficient clinical data and is in compliance with the relevant CS.**
- **For devices belonging to WET the clinical evaluation can be based on data pertaining to similar devices.**
- **For WET devices characterized by low risk and by a little evolution in the state of the art, the clinical evaluation can be mainly supported by data coming from PMS.**

8 Demonstration of conformity based on non-clinical data

In exceptional cases, MDR Art. 61(10) – as also previously reported by MEDDEV 2.7/1 and by MDD Annex X (1.1d) – states that for devices other than class III and implantable devices, a clinical investigation may not be required where the demonstration of conformity with GSPR based on clinical data is not deemed appropriate.
In these cases:

- preclinical data can serve the purpose of demonstrating conformity with the GSPR, including performance evaluation, bench testing and preclinical evaluation (e.g., simulated use, animal testing, cadaveric testing, etc.), and
- an adequate justification shall be given and documented in the device's technical documentation, based on the results of the risk management activities and considering the interaction between the device and the human body, its claims, and the clinical performance intended.

In any case, MDCG 2020-6 guidance clarifies that where preclinical testing is used for confirmation of safety and performance and initial conformity assessment, PMCF studies may be undertaken to confirm these conclusions.

9 Post-market clinical follow-up (PMCF) requirements

According to MDR (Art. 83), all manufacturers shall establish a comprehensive PMS system set up under their QMS (Art. 10).
The MDR defines "post-market surveillance" as all activities carried out by manufacturers in cooperation with other economic operators to institute and keep up to date a systematic procedure to proactively collect and review experience gained from devices they place on the market, make available on the market or put into service for the purpose of identifying any need to immediately apply any necessary corrective or preventive actions (Art. 2(60)).
In the context of PMS activities, the MDR considers the PMCF as a continuous process that updates the clinical evaluation, and that shall be addressed in the PMS plan.
The MDR does not newly introduce the concept of PMCF[5], but definitely reinforces it devoting part B of Annex XIV to it. In particular, the MDR reiterates the fact that PMCF shall be performed pursuant to documented methods laid down in a PMCF plan, and provides a set of minimum contents for developing the plan[6]. It also specifies that the findings of the PMCF shall be analyzed and documented in a PMCF evaluation report[7], which constitutes part of the clinical evaluation report and technical documentation.

[5] The requirement for PMCF was already established by the medical devices Directives (e.g., Annex X, 1.1c). However, no clear definition of PMCF was provided. It was MEDDEV 2.12-2 rev.2 issued in 2012 to provide more details on the conduction of PMCF activities, as well as clarifying the elements of PMCF studies, the circumstances where these are indicated, their objectives and designs.

[6] MDCG 2020-7 guideline has been issued in April 2020 on PMCF Plan template.

[7] MDCG 2020-8 guideline has been issued in April 2020 on PMCF Evaluation Report template.

On how to conduct the PMCF, MDR Part B of Annex XIV states:
*"(...). When conducting PMCF, the manufacturer shall **proactively** collect and evaluate clinical data from the **use in or on humans** of a device **which bears the CE marking** and is placed on the market or put into service within its intended purpose as referred to in the relevant conformity assessment procedure, with the aim of confirming the safety and performance throughout the expected lifetime of the device, of ensuring the continued acceptability of identified risks and of detecting emerging risks **on the basis of factual evidence**".*

First, it is clarified that PMCF data shall pertain to a CE-marked device. In this regard, to comply with the MDR "clinical data" definition, that means that post-market clinical data must be produced/ collected on the device object of the evaluation and/or – if present – on a CE-marked medical device for which equivalence has been demonstrated under MDR. This is believed to impact significantly on manufacturers' PMCF activities, if it is considered that PMCF conducted under the old regimen was usually and uniquely based on literature review, updating state of the art and the data pertaining to safety and performance of similar products, or if available, equivalent device(s).

Clinical data on legacy devices should have collected in the post-market phase. Still, in the event that post-market clinical data is not adequately comprehensive to provide sufficient clinical evidence, and the demonstration of equivalence is no longer possible under MDR, new data may need to be generated prior to CE-marking under the MDR, so post-market clinical investigations (or at least real-world data collection) may probably need to be conducted on the device concerned.

Importantly, the MDR specifies that clinical data collected post-market as part of PMS activities has to be based on factual evidence, meaning that it has to refer to the actual use of a CE-marked device in or on humans. Consistently, an important requirement of the MDR, as detailed in Annex XIV (Part A), is to include in the clinical evaluation plan a clinical development plan (CDP). The CDP shall indicate the progression from exploratory investigations - such as first-in-man, feasibility and pilot studies - to confirmatory investigations - such as pivotal clinical investigations and PMCF.

Take-home messages

- **PMCF activities have to be planned. The PMCF plan, which basic requirements are defined in the MDR, shall be part of the PMS plan.**
- **The findings of PMCF activities are to be recorded and documented in a PMCF Evaluation Report.**
- **PMCF is a proactive source of data for PMS, and data collected have to be based on factual evidence, i.e., on the actual use in/on humans of CE-marked devices. To comply with the MDR definition of "clinical data", CE-marked devices to which the MDR refers can only be the device concerned and/or the equivalent device, if present.**
- **Because PMCF is not a new concept (already required by MDD and defined by MEDDEV 2.7/1 rev.4 and MEDDEV 2.12-2 rev.2), legacy devices should have collected clinical data in the post-market phase. However, PMCF activities under the old Directives were not usually based on real-world data collection or post-market clinical investigations on the device concerned. The production of new PMCF data may be needed prior to CE-marking under the MDR.**

News: ISO/TR 20416 on medical device post-market surveillance is under review and will be published soon. This could be used as a reference for planning and implementing PMS and PMCF activities adequately.

10 Clinical data requirements for legacy devices under MDR

As previously discussed, the MDR reinforces a number of important concepts, such as the incorporation of PMS and PMCF in the process of clinical evaluation. Legacy devices are not exempted from these additional requirements. It is however specified that, even during the period of validity of their MDD certificates, the new requirements for PMS (and PMCF) will apply from 26 May 2021, DoA of the MDR.

When it comes to the first MDR conformity assessment of a legacy device, the pre-market and post-market clinical data generated for the purpose of MDD constitute the basis of the clinical evaluation process under the MDR. However, the clinical data used for conformity assessment under MDD does not necessarily provide sufficient clinical evidence under MDR. Also, although the Directives indicate that data shall be collected in the post-market phase for all devices, in practice data collected may not meet the MDR criteria.
For these reasons, manufacturers should conduct a gap analysis with respect to the MDR requirements, in order to determine if additional data to support clinical evidence is required. When assessing the conformity of legacy devices under the MDR, it is important to take into account the following aspects:

- When clinical evaluation was based on the equivalence route, equivalence will have to be confirmed and demonstrated according to the MDR requirements.
- Whether PMCF studies under the MDD have been – properly – conducted.
  As noted by MEDDEV 2.12-2 on PMCF, especially in cases where the clinical evaluation under MDD was based exclusively on clinical data from an equivalent device for initial conformity assessment, PMCF studies would have to be conducted.
- The MDR does not allow unpublished reports on other clinical experience to contribute to the clinical evaluation.

It has to be taken into account that MEDDEV 2.7/1 rev. 4 guideline on medical devices' clinical evaluation already specified that reports on clinical experience not adequately supported by clinical data (such as many anectodal reports, experts' opinions, etc.) may only contribute to the clinical evaluation as indirect supportive data, to help – for example – in the identification of clinical risks: however, these should not be used to directly proof the adequateness of a device's performance and safety. This is another important aspect to be taken into account when updating legacy devices' clinical evaluation.

Based on the results of the gap analysis, in some cases it would be necessary for the manufacturer to undertake PMCF studies to generate new data for legacy devices before CE marking under the MDR. For this purpose, MDCG 2020-6 specifies that controlled clinical investigations are generally the preferred method for collecting clinical data as part of the PMCF studies for some products. Other possibilities to gather relevant clinical data to bridge the gap are systematic reviews of data published in the literature and the evaluation of results from PMS activities, such as clinically relevant scientifically sound questionnaires or registries. With respect to the use of PMS data for the purpose of conformity assessment, MDCG 2020-6 states that the use of uncontrolled sources of clinical data – such as complaints or incident reports – is generally considered insufficient to provide proof of

safety, and should be limited to cases where data from pre- or post-market clinical investigations - or other PMCF studies - are not deemed appropriate.

Take-home messages

- **Legacy devices are not exempted from MDR's PMS and PMCF requirements, which become mandatory from 26 May 2021.**
- **The pre- and post-market clinical data used for conformity assessment under the Directives constitute the basis for the clinical evaluation of legacy devices under the MDR. However, it shall be verified that sufficient clinical evidence is provided under MDR. A gap analysis should be conducted for this purpose.**
- **It may be possible that - for devices that were equivalent under MDD and according to MEDDEV 2.7/1 rev.4 clinical, technical and biological characteristics - equivalence cannot be confirmed under MDR. Data from those devices cannot contribute to the clinical evaluation.**
- **It shall be verified that PMCF studies have been properly conducted for legacy devices, unless a proper justification exists. If the clinical data on the device itself (including PMCF) is not adequate or not comprehensive enough to provide sufficient clinical evidence under the MDR, new data may need to be generated before CE-marking.**

11 Tips and recommendations: what to improve in your clinical evaluations

On the basis of our experience and on the MDR requirements on clinical evaluation, we have compiled these tips and recommendations for the improvement of your clinical evaluations:

1. Conduct a detailed **gap analysis** with respect to new provisions, in order to determine whether the existing clinical data are sufficient to verify that your device is in conformity with the MDR requirements.

2. Prepare "ad hoc" **clinical evaluation plans (CEP)**: clinical evaluation has to be planned, and pertinent data identified. Due to the wide variety of medical devices, the CEP cannot be a standard template: it has to be designed on a case-by-case basis. The structure and the content of the CEP depend, among other factors, on the device's classification and risk profile, on the design and technology on which the device is based, on its life cycle stage, and on the presence or absence of an equivalent device.

3. Plan **traceable and reproducible literature searches**: it is recommended that the search for current knowledge/state of the art literature is planned and documented.

4. Plan for the future: **prepare post-market surveillance (PMS) plans, including post-market clinical follow-up (PMCF) plans, in advance**: you should be ready with your PMS and PMCF plan before submitting the technical documentation to a Notified Body.

4. Prepare a **Clinical Development Plan (CDP)** to be included in your clinical evaluation plan. The CDP will also have to take into account PMCF studies' planning.

12 Conclusions

Regardless of the size of a company's business or on the types and classes of medical devices that it develops, complying with the new MDR requirements will require significant investments for manufacturers. In particular, to be aligned with MDR clinical data provisions, adequate resources and proper competences shall be allocated for initial CE-marking and certification maintenance.
The equivalence route has been made less accessible by MDR, and it has to be taken into account that the new definition of "clinical data" excludes unpublished reports on other clinical experience gained on medical devices; this will have a major impact on the clinical evaluation of both "ex novo" and legacy devices.
In 1MED, thanks to our extensive experience in clinical evaluations and equivalence determination, we can help you understand what clinical data are needed to comply with MDR requirements for clinical evidence, as well as to bridge the gap with respect to clinical data requirements for your legacy devices, and with the design of a proper data collection strategy.
We can also support you in conducting clinical investigations and updating clinical evaluations throughout the entire life cycle of your medical devices.

For more information on our regulatory and clinical services, please visit: https://1med.ch

References

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- Regulation (EU) 2020/561 of the European Parliament and of the Council of 23 April 2020, amending Regulation 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC;

- ISO 14971:2019 - Medical devices – Application of Risk Management to medical devices;

- ISO 10993-1:2018 – "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process";

- MEDDEV 2.7/1:2016 rev. 4 - Clinical evaluation: a guide for Manufacturers and Notified Bodies under Directive 93/42/EEC and 90/385/EEC;

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- IMDRF MDCE WG/N56FINAL:2019 (formerly GHTF/SG5/N2R8:2007) – Clinical Evaluation (October 2019);

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- MDCG 2020-5: Clinical Evaluation – Equivalence: A guide for manufacturers and notified Bodies (April 2020);

- MDCG 2020-6: Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC: a guide for manufacturers and notified bodies (April 2020);

- MDCG 2020-7: Post-market clinical follow-up (PMCF) Plan Template: a guide for manufacturers and notified bodies (April 2020);

- MDCG 2020-8: Post-market clinical follow-up (PMCF) Evaluation Report Template: a guide for manufacturers and notified bodies (April 2020).

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