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Clinical Conformity Routes for Orthopaedic Devices

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Structure of this talk

1) Setting the stage (prerequisites, ground rules of MDR, list of available routes)
2) Description of each route's expectations to reach initial conformity
3) Description of PMCF expectations for each route
4) Real-life examples for each route
5) Summary and open questions

General expectation of MDR

Article 61 states that:

“In the case of implantable devices and class III devices, clinical investigations shall be performed”

However, multiple exceptions are listed in certain sections of Article 61 and guidance documents.

Important Questions (to choose applicable route of conformity)

1) What risk class is my device?
2) Is my device implantable?
3) Is my device exempted? (not to confuse with WET!)
4) Is my device a legacy device already certified under previous Directive?

Choose 1 of the following routes, not multiple!

- Article 61 (4)
- Article 61 (5)
- Article 61 (6a)
- Article 61 (6b)
- Article 61 (10)
- MDCG 2020-6
- (pre-market, pivotal) Clinical Investigation

Article 61 (4) – equivalence to own device

4. In the case of implantable devices and class III devices, clinical investigations shall be performed, except if:

— the device has been designed by modifications of a device already marketed by the same manufacturer,

— the modified device has been demonstrated by the manufacturer to be equivalent to the marketed device, in accordance with Section 3 of Annex XIV and this demonstration has been endorsed by the notified body, and

— the clinical evaluation of the marketed device is sufficient to demonstrate conformity of the modified device with the relevant safety and performance requirements.

- Modification of already marketed device of same manufacturer
- Demonstrate equivalence in line with MDCG 2020-5
- Sufficient clinical data on the proposed equivalent device needs to be presented

Article 61 (4) – PMCF needs

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.

- Clear expectation that a PMCF study is necessary to confirm initial equivalence assumption
- Study needs to be aligned with Annex XV of MDR (alternatively ISO 14155 + gap analysis)

Article 61 (4) – example

Titanium Lumbar cage

- Risk class? - **III**, Implantable? – **Yes**, Exempted? – **No**, Legacy Device? - **No**
- Bullet shaped version already on the market under MDD
- New banana shaped version now added to portfolio

→ Equivalence approach to own device in line with MDCG 2020-5 was acceptable
→ Clinical data on **bullet shaped cage** deemed sufficient to support p&s over proposed lifetime of device
→ PMCF study plan submitted and fulfilled expectations of Annex XV

Article 61 (5) – equivalence to competitor device

5. A manufacturer of a device demonstrated to be equivalent to an already marketed device not manufactured by him, may also rely on paragraph 4 in order not to perform a clinical investigation provided that the following conditions are fulfilled in addition to what is required in that paragraph:

— 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 ongoing 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.

- Demonstrate equivalence in line with MDCG 2020-5
- Sufficient clinical data on the proposed equivalent device needs to be presented
- Contract needs to be in place!
- Evidence of compliant Clinical Evaluation of equivalent device → MDR certificate?

Article 61 (5) – PMCF needs

- Ensure and demonstrate ongoing access to TD of competitor mandatory
- PMCF Study required → needs to be aligned with Annex XV of MDR (alternatively ISO 14155 + gap analysis)

Paragraph 5 by itself → No direct mentioning that a PMCF study is necessary to confirm initial equivalence assumption, BUT!

"….**in addition** to what is required in paragraph (4)"

AND! MEDDEV 2.12/2 rev.2 also still applicable

Article 61 (5) – example

Article 61 (6a) – „legacy device“ with sufficient CD available

6. The requirement to perform clinical investigations pursuant to paragraph 4 shall not apply to implantable devices and class III devices:

(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 CS for the clinical evaluation of that kind of device, where such a CS is available; or

- MUST have been certified under MDD
- AND clinical data on the device deemed sufficient
- AND in compliance with Common Specifications (so far not applicable)

Article 61 (6a) – PMCF needs

6.2. The PMCF plan shall include at least:

(a) the general methods and procedures of the PMCF to be applied, such as gathering of clinical experience gained, feedback from users, screening of scientific literature and of other sources of clinical data;

(b) the specific methods and procedures of PMCF to be applied, such as evaluation of suitable registers or PMCF studies;

- Since clinical data on such a device shall be sufficient, only the basic PMCF requirements from Annex XIV Part B apply
- That includes certain specific methods of PMCF (i.e. proactive clinical data collection) → open to interpretation (depending on open questions, lifetime of the device, etc.)

Article 61 (6a) – example

Titanium intramedullary tibia nail

- Risk class? - **IIb**, Implantable? – **Yes**, Exempted? – **No**, Legacy Device? - **Yes**
- Already on the market under MDD for decades
- No significant design changes compared to last certification
- Clinical data based on > 30 peer-reviewed publications, 4 manufacturer-initiated PMCF studies

→ Last MDD certificate was provided

→ Clinical data on actual device deemed sufficient to support p&s over entire lifetime of device (18 month)

→ PMCF Plan fulfilled expectations of Annex XIV Part B, offering data collection through internal registry (specific PMCF) and continued literature search (general PMCF)

Article 61 (6b) – exempted devices

6. The requirement to perform clinical investigations pursuant to paragraph 4 shall not apply to implantable devices and class III devices:

(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, where such a CS is available.

- Must clearly fall within the listed devices (!Careful with descriptions! - intramedullary nail is not a wire; a spinal cage is not a wedge)
- Sufficient clinical data on the actual device still expected, just not CI as a data source
- AND in compliance with Common Specifications (so far not applicable)

Article 61 (6b) – PMCF needs

6.2. The PMCF plan shall include at least:

(a) the general methods and procedures of the PMCF to be applied, such as gathering of clinical experience gained, feedback from users, screening of scientific literature and of other sources of clinical data;

(b) the specific methods and procedures of PMCF to be applied, such as evaluation of suitable registers or PMCF studies;

- Since clinical data on the device apparently sufficient, only the basic PMCF requirements from Annex XIV Part B apply
- That includes certain specific methods of PMCF (i.e. proactive clinical data collection) → open to interpretation (depending on open questions, lifetime of the device, etc.)

Article 61 (6b) – example

Newly developed K-wires

- Risk class? - **IIb**, Implantable? – **Yes**, Exempted – **Yes**, Legacy Device - **No**
- Initial certification/addition to existing QMS certificate
- Internal patient data collection (interim report, BUT no Annex XV-compliant Investigation) → no serious AEs, performance outcome achieved in >95% of patients

→ Agreement on exemption status
→ Clinical data deemed sufficient to initially support p&s
→ PMCF plan fulfilled expectations of Annex XIV Part B, describing ongoing data collection and defining milestones until final report (specific PMCF) and continued literature search (general PMCF)

Article 61 (10) – devices where Clinical Data is not appropriate

10. Without prejudice to paragraph 4, where the demonstration of conformity with general safety and performance requirements based on clinical data is not deemed appropriate, 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 performance intended and the claims of the manufacturer. In such a case, the manufacturer shall duly substantiate in the technical documentation referred to in Annex II why it considers a demonstration of conformity with general safety and performance requirements that is based on the results of non-clinical testing methods alone, including performance evaluation, bench testing and pre-clinical evaluation, to be adequate.

- Mostly non-implantables and IIa devices
- A justification from the manufacturer (why CD expectation is not appropriate) must be provided after risk assessment AND NB has to agree
- Pre-clinical data and bench tests still need to be summarized in CER and references made available to allow verification

Article 61 (10) – PMCF needs (Annex VII)

4.5.5. Clinical evaluation assessment

The notified body's assessment of clinical evaluations as referred to in Annex XIV shall cover:

justifications in relation to non-performance of clinical investigations or PMCF.

- If clinical data to support a certain device is deemed inappropriate and Notified Body agrees

→ Annex VII allows "non-performance" of PMCF that needs to be duly justified

Article 61 (10) – example

Stainless Steel Rasp for hip replacement

- Risk class? - **IIa**, Implantable? – **No**, Exempted? – **No**, Legacy Device? - **Yes**
- Necessary to open bone canal before implantation
- Associated with certain implants (alternative: leverage implant's CD to indirectly support rasp)
- Provided risk analysis and bench tests + sales & complaint data

→ Agreement on justification for not relying on CD
→ Bench testing and PMS data deemed sufficient to support p&s
→ PMCF plan fulfilled expectations (describing continued literature search for SOTA on hip replacement procedure (general PMCF) and justifying why specific PMCF not needed)

MDCG 2020-6 – legacy devices without sufficient CD

Clarification of terminology

Legacy devices:

- this is considered to include all devices previously CE marked under the European Medical Devices Directive 93/42/EEC (MDD) or Active Implantable Medical Devices Directive 90/385/EEC (AIMDD)

MDCG 2020-6 – legacy devices without sufficient CD

Clarification of terminology

Well-established technologies

The common features of the devices which are **well-established** technologies are that they all have:

- 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;
- well-known clinical performance characteristics and their generic device group are standard of care devices where there is little evolution in indications and the state of the art;
- a long history on the market.

MDCG 2020-6 – legacy devices without sufficient CD

> Class III legacy devices and implantable legacy devices which are not well-established technologies should have sufficient clinical data as a minimum at level 4. Those devices which are well-established technologies may be able to confirm conformity with the relevant GSPRs via an evaluation of cumulative evidence from additional sources as listed below. Reliance solely on complaints and vigilance is not sufficient.

- Level 1-4 data sources: CIs, high quality registries, peer-reviewed publications
- Additional sources: Equivalence, SOTA and CD from similar devices, Complaints & Vigilance, cadaver & animal tests, etc.
- → "poor man's equivalence approach" or "extension of grace period"

MDCG 2020-6 – PMCF needs

Manufacturers should conduct a gap analysis with respect to the MDR requirements. If data gaps have been identified, there are different possibilities to bridge those gaps.

While controlled clinical investigations might be the preferred method for collecting clinical data as part of the PMCF studies for some products, there are other possibilities to gather relevant clinical data in the field in order to close the clinical data gap. Other alternatives include, but are not limited to systematic reviews of clinical data published in the literature, evaluation of results from PMCF studies such as clinically relevant scientifically sound questionnaires[51] or registries. Scientifically sound studies will normally include (note, this

- Clinical data gap analysis expected
- Clear and reliable PMCF Plan on how the data gaps can be closed
- Often includes a PMCF study to confirm the assumption that a device performs similar to generic device group
- Registry data can be helpful in long-term data gap situations

MDCG 2020-6 – example

Titanium-sprayed, HA coated femoral stem

- Risk class? - **III**, Implantable? – **Yes**, Exempted? – **No**, Legacy Device? - **Yes**
- Initial certification under MDD decades ago, based on equivalence, now NB closed and transfer to TÜV SÜD, sold mostly in smaller markets
- no publications, no CI, no suitable registry data, no PMCF studies

→ Agreement on Legacy and WET status (MDD certificate AND justification!)
→ Through SOTA search, Clinical data from **similar** devices presented and accepted to support p&s → data sources need to be verified by NB!
→ PMCF **Study** Plan fulfilled expectations of Annex XV, describing long-term data collection (10 years), acceptable outcome parameters and sample size
→ In addition, cooperation with local registry and continued literature search (general PMCF)

Annex XV – Clinical Investigations

ANNEX XV

CLINICAL INVESTIGATIONS

Article 62

General requirements regarding clinical investigations conducted to demonstrate conformity of devices

1. Clinical investigations shall be designed, authorised, conducted, recorded and reported in accordance with the provisions of this Article and of Articles 63 to 80, the acts adopted pursuant to Article 81, and Annex XV, where carried out as part of the clinical evaluation for conformity assessment purposes, for one or more of the following purposes:

→ Be aware of applicability of Articles 62 - 81

→ EN ISO 14155 acceptable standard if gap analysis is provided

Annex XV – PMCF needs

- Clinical data gap analysis expected
- Clear and reliable PMCF Plan on how the data gaps can be closed
- Often includes a PMCF study to confirm the initial results in a wider population over entire lifetime of device
- Registry data can be helpful in long-term data gap situations

Annex XV – example

Hip resurfacing implant

- Risk class? - **III**, Implantable? – **Yes**, Exempted? – **No**, Legacy Device? - **No**
- This was initial certification. Not on the market elsewhere, no MDD certificate

→ Pivotal (pre-market) Clinical Investigation was necessary and initiated
→ CIP, CIR, CRFs, Ethics vote & Registration, etc. were submitted and assessed
→ Critical s&p outcome parameters were supported with CD on an adequate patient number with up to 3-year FU
→ Transition of CI into PMCF study with 10-year FU planned
→ In addition, cooperation with well-known & **reliable** registries (NJR, EPRD) and continued literature search (general PMCF) proposed

Summary

To reach conformity with CD expectations:

- ❑ Answer the 4 questions
- ❑ Carefully choose **1!** appropriate route
- ❑ Be aware of specific expectations/requirements for that route
- ❑ Plan adequate PMCF activities that fit your route and close the data gaps your device might have

Thank you!

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