The European Association of Medical devices Notified Bodies

Team-NB Position Paper

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Clinical Evaluation Based on Non-Clinical Data: EU Medical Device Regulation 2017/745 Article 61.10

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Aim

In this paper we aim to outline the approach taken by the notified body when considering the acceptability of a manufacturer's justification for relying on non-clinical data for the purpose of demonstrating safety and performance of a device. It is envisaged that this paper will support manufacturers with their decision-making process regarding applicability of Article 61(10) and will also provide guidance on best practice for preparing a robust justification for its use.

Introduction

MDR Article 61(1) establishes the general rule that confirmation of conformity with the relevant General Safety and Performance Requirements (GSPRs) – including the evaluation of undesirable side-effects and of the acceptability of the benefit–risk ratio under normal conditions of the intended use – shall be based on clinical data providing sufficient clinical evidence. This reflects that the intended purpose defines the clinical context within which conformity, clinical safety and benefit–risk acceptability shall be assessed, and that the evaluation of side-effects and benefit–risk parameters is intrinsically linked to that intended purpose.

Article 61(10) is an exceptional pathway that only modifies the type of data used, not the purpose or objectives of the clinical evaluation. The difference is that, in the specific cases covered by Article 61(10), these same objectives may be achieved using a sufficiently robust body of non-clinical evidence, provided the manufacturer can justify that clinical data are not appropriate for verifying the predefined safety, performance and benefit–risk criteria:

1. The manufacturer defines the intended purpose in accordance with Article 2(12) and Annex II Section 1.1, 23(4) of the MDR. *(Meddev 2.7.1/Rev.04, A3 provides further guidance on the elements of the intended purpose[1]).*

   On this basis and considering the relevant GSPRs, the following are identified:
   - indications, contra-indications, the patient target group(s) and intended users
   - the relevant side-effects and other clinically relevant risks,
   - the intended clinical benefits with relevant outcome parameters, and
   - the state-of-the-art-based parameters and acceptance criteria for determining acceptability of the benefit–risk ratio.

2. For each identified parameter, the manufacturer must specify the corresponding measurement method (clinical versus non-clinical) that would be considered appropriate according to state of the art.

   The decisive regulatory question is whether the appropriate method for measuring and substantiating these identified parameters materially depends on clinical data — that is, on safety or performance information generated from use of the device (or an equivalent device) in its intended clinical context within the meaning of Article 2(48).

[1] Refer to IMDRF/SaMD WG/N81 FINAL: 2025 for Software

- Where verification of parameters materially depends on such clinical data, the clinical evaluation is considered to be based on clinical data, and Article 61(1) applies.

- Where those parameters can be adequately evaluated through validated non-clinical methods and the overall benefit–risk conclusion does not depend at all on clinical data within the meaning of Article 2(48), reliance on Article 61(10) can be justified. In this case, non-clinical data may be obtained from the following sources:
    - Simulated use / animal / cadaveric testing involving healthcare professionals or other end users
    - Pre-clinical and bench testing / compliance to standards
    - Performance evaluation / in vitro/ ex vivo/ in silico testing/ computational modelling/ pre-clinical evaluation

To avail themselves of the clinical data exemption provided by Article 61(10), manufacturers must provide a justification which clearly outlines why clinical data is not considered appropriate for measuring and substantiating the identified safety and performance parameters. As a general rule, this will need to be established through the process of clinical evaluation and the justification presented within the clinical evaluation section of the technical documentation.

Once marketed, clinical data generated from actual use of the Article 61(10) device and collected via the manufacturers PMS/PMCF system (e.g complaints and vigilance data, user surveys), may be used to update the clinical evaluation throughout the lifetime of the device. However, the mere existence of limited or ancillary clinical data, does not, by itself, preclude the application of Article 61(10); the decisive question is whether demonstration of conformity based on non-clinical data is appropriate. For devices justified under Article 61(10), clinical data is not the primary basis for initial conformity but can become important for confirming ongoing safety and performance and for reassessing whether the Article 61(10) justification remains appropriate.

A specific list of Article 61(10) devices comparable to the list of WET devices provided by Article 61.6.(b) is not feasible: Depending on its specific defined intended purpose, even very “simple” non-implantable class IIa/IIb devices can be used in a wide and diverse range of potential clinical applications, and may or may not be accompanied by explicit clinical claims. As a result, the specific device or generic device group does not, on its own, define the applicability of Article 61(10), but instead the applicability is determined by the multiple facets of a device’s intended purpose and individual clinical evaluation. Thus, acceptability of the manufacturer’s justification for generating a clinical evaluation based on non-clinical data alone needs to be considered by the notified body on a case-by-case basis.

Manufacturer Justification

To avail of clinical data exemption provided by Article 61(10) for class I/IIa/IIb non-implantable devices, the manufacturer must provide a justification which considers the results of risk management, intended clinical performance, claims and the specifics of the device interaction with the human body. The justification should be sufficiently detailed to enable persons not themselves involved in the clinical evaluation to understand how the manufacturer reached the conclusion that clinical data are **not appropriate** (i.e., clinical data is "not available" or "difficult to generate" are not valid arguments) for demonstrating safety and performance of the specific device.

Defining the state of the art plays a decisive role in any justification under Article 61(10). It determines which safety and performance parameters are relevant for the device's intended purpose and, critically, whether these parameters are normally verified through clinical outcomes in humans or can be adequately assessed by non-clinical methods.

Caution is advised in cases where the manufacturer intends to define their safety and performance parameters solely based on the generic device group. While the generic device group is relevant for the definition of well-established technologies according to MDCG 2020-6, as previously discussed, due to the wide range of clinical applications that lower risk devices are used for, it is typically more appropriate to define the safety and performance parameters at the device level in the case of Article 61.10.

Where state of the art indicates that achievement of the intended clinical objective–for example treatment of a disease, reduction of symptoms or complications, or improvement of diagnostic accuracy–is demonstrated through safety or performance information that is generated from the clinical use of the device (or an equivalent device) in its intended clinical context, confirmation of conformity must depend on clinical data within the meaning of Article 2(48). In such cases, the clinical evaluation shall be based on clinical data in accordance with Article 61(1).

Article 61(10) may only be justified where, for the specific intended purpose, state of the art demonstrates that all critical safety and performance parameters can be reliably verified by validated non-clinical methods, and where the determination of an acceptable benefit–risk profile does not depend on clinical data in current medical practice.

For some devices, it may be possible to use non-clinical data alone for confirmation of performance endpoints and still use clinical data for confirmation of specific safety endpoints and vice versa. However, this is not considered conducive to an Article 61(10) approach.

Manufacturer Justification – What does the Notified Body look for?

As part of the conformity assessment, the role of the notified body is to assess the adequacy of the manufacturers' justification and the available body of non-clinical evidence. Article 61(10) requires the justification to address the following criteria: intended clinical performance and claims, interaction between the device and the human body and risk management. In this section, we will expand on each of the criteria to demonstrate the level of information which is needed to enable the notified body to assess the adequacy of the justification. Importantly, the decision on whether the justification is acceptable is based on consideration of all the criteria together, rather than in isolation.

Intended Clinical Performance and Claims:

The notified body seeks to understand how the device works within the clinical setting, whether its performance is critical to success of the diagnostic or therapeutic intervention and how it leads or contributes towards an improvement in patient health.

Whilst not exhaustive, the following questions may be useful for the manufacturer to consider when documenting this part of the justification:

1. Clearly describe the role of the device within the clinical setting
    - In general, the less integral to the success of the diagnostic or therapeutic intervention, the more likely Article 61(10) will be applicable. For example, Article 61(10) may be more applicable to an accessory to a medical device which does not impact the achievement of health outcomes for the patient
2. How does the device achieve its intended purpose?
    - The less that individual patient characteristics influence the successful achievement of a device's intended purpose, the more likely Article 61(10) will be applicable
3. How does the device contribute to a positive impact on the health of an individual or a positive impact on patient management or public health and how will that impact be demonstrated?
    - The greater the potential impact on health outcomes, the less likely that Article 61(10) will be applicable.
4. What actions are triggered by the information provided by the device and how soon will the information be acted on?
    - Article 61(10) is more likely to be applicable to a device which does not trigger an immediate patient treatment decision or action
5. How is it demonstrated that the device performs favorably when compared to state of the art?
    - Article 61(10) is unlikely to be accepted if the state of the art safety and performance endpoints are defined by clinical data
6. Are there any explicit clinical claims (e.g., "This device will reduce pain") or implicit clinical claims that can only be confirmed by clinical data? Implicit claims are claims that are not explicitly stated by the manufacturer, but are obvious from the state of the art, e.g. a manufacturer only states that a TENS (Transcutaneous Electrical Nerve Stimulation) device is intended to create electric pulses, but it is obvious from the state of art that this would always be used for pain control.
    - If "Yes", Article 61(10) is not applicable as clinical data is required to support clinical claims
7. Are the results of the non-clinical performance testing representative of all possible disease states, scenarios where the device is used, tissue types, patient population, users, etc. that the device is likely to interact with?
    - If "Yes", Article 61(10) becomes more applicable

Key Point: Ultimately this part of the justification should enable the assessment team to understand the intended clinical benefits arising from the device's intended purpose, the predefined parameters which allow for assessment of those benefits and the measurement methods required to verify those parameters. It is not acceptable to state that the device does not provide any clinical benefit, as this would ultimately mean that the clinical evaluation cannot conclude that the benefits of using the device outweigh the residual risks.

Device and Human Body Interaction

The notified body seeks to understand how the device interacts with the human body, including the nature and extent of the contact. It is important to note that interaction may not be limited to bodily contact. For example, in the case of AI devices which interact with cognitive processes.

Whilst not exhaustive, the following questions may be useful for the manufacturer to consider when documenting this part of the justification:

1. How invasive is the device?
    - The more invasive, the less likely Article 61(10) will be applicable
2. What type of body tissue or anatomical location does the device interact with?
    - The more sensitive or vital the tissue, the less likely Article 61(10) will be applicable
3. Is the device in contact with injured or intact skin or mucous membranes?
    - If there is no contact at all or only contact with intact skin, Article 61(10) is more likely to be applicable. Long term physical contact or invasiveness to injured skin or mucous membrane will usually contradict the applicability of Article 61(10) because it would be associated with clinically relevant risks such as allergic reactions, tissue damage, etc.
4. What is the duration of interaction between the device and the human body?
    - The shorter the duration, the more likely Article 61(10) will be applicable
5. Which is the anatomic region of contact?
    - Devices intended specifically for use in direct contact with the central nervous system, heart, or circulatory system are not applicable for Article 61(10) due to the classification rules of MDR Annex VIII
6. What are the worst-case clinical risks associated with the anatomical location(s) or body tissues that the device interacts with?
    - The less relevant, the more likely Article 61(10) will be applicable
7. If the device contacts the human body, can the results of non-clinical testing methods be extrapolated to demonstrate that there is no negative impact on the patient?
    - If “Yes”, this makes the applicability of Article 61(10) more possible
8. Does the device interact with the human body in a manner that directly modifies physiological processes or tissue function?
    - If “Yes”, this makes the applicability of Article 61(10) less likely
9. Is the safety or performance of the device materially dependent on biological responses that cannot be fully predicted or characterized through non-clinical methods?
    - If “Yes”, this makes the applicability of Article 61(10) less likely
10. Does interaction with the human body introduce patient-specific variability?
    - If “Yes”, this makes the applicability of Article 61(10) less likely
11. Is the device under assessment part of a system or stand-alone?
    - The more central the device is to the ability of the system to achieve its intended purpose, the less likely Article 61(10) would apply

12. Is there sufficient information regarding the device and human body interaction available from sources other than clinical data?
    - If “Yes”, this makes the applicability of Article 61(10) more likely

Risk Management

The notified body seeks to understand the risks to patient safety and/or the user resulting from use of the device, and whether these are well understood and accepted by the medical community.

Whilst not exhaustive, the following questions may be useful for the manufacturer to consider when documenting this part of the justification:

1. Considering state-of-the-art, what are the potential and what are the worst possible device related harms and residual clinical risks?
    - The more clinically relevant, the less likely Article 61(10) will be applicable
2. Are the results of the non-clinical safety testing representative of all possible disease states, tissue types, patient population, users, etc. that the device may interact with?
    - If “Yes”, it is more likely that Article 61(10) is applicable
3. After all residual risks have been reduced as far as possible, is clinical data required to determine if they are acceptable considering the device’s benefits?
    - If “Yes”, Article 61(10) is unlikely to apply

Key Point: Ultimately, this part of the justification should enable the assessment team to understand how the results of non-clinical testing methods alone unequivocally demonstrate that (i) the measures taken to control clinical risks are effective when the device is used as intended, and (ii) additional clinical testing from use of the device in/on patients would not provide any useful safety information. In such instances, it a summary of clinically relevant risks in the clinical evaluation–with an outline of how these have been mitigated through design controls and non-clinical testing–is likely to support a justification regarding the applicability of Article 61(10).

Article 61.10: Clinical Evaluation Documentation

Considering that the MDR does not differentiate between Article 61(10) and non-Article 61(10) devices when it comes to the requirements for clinical evaluation documentation, Article 61(10) devices are expected to be supported by a complete clinical evaluation, including post market surveillance, documentation package. The only exception is that the conduct of specific PMCF is typically not expected for Article 61(10) devices and this should be justified within the PMS plan per MDR Annex III, Section 1.1 b. General PMCF activities defined according to MDR Annex XIV, 6.2.(b) are usually required.

Article 61.10: Common Deficiencies Identified by the Notified Body

Common Deficiencies in State-of-the-art Analysis

- State-of-the-art analysis is not included in the CER
- The state-of-the-art analysis does not clearly define which meaningful safety and performance parameters are expected to be measured in line with evidence-based medicine
- Manufacturer does not consider clinical data currently available for similar devices
- Clinical risks are not fully defined based on the state of the art

Key Point: State-of-the-art analysis is critical for defining the safety and performance parameters which require support from non-clinical data and for supporting the manufacturers justification that clinical data is not appropriate. It must be comprehensive and allow the identification of parameters which enable comparison of the subject device to similar devices.

When defining state-of-the-art, it's important to consider the role of the device in the clinical procedure/intervention including its criticality to success, and the potential clinical impact on the patient if the device does not perform as intended (e.g., intra-operative complications, extended surgery time, implant failure, misalignment of or incorrect position of accompanying devices).

If the analysis demonstrates that clinical data is available for similar devices including the generic device group, it may prove challenging to justify that Article 61(10) is applicable. Refer to the manufacturer's justification section of this paper for guidance.

Common Deficiencies in Manufacturer's justification

- Manufacturer's justification is limited to a reiteration of the wording of MDR Article 61(10) and does not expand on the listed criteria or clearly explain why clinical data is deemed to be not appropriate
- Manufacturer applies Article 61(10) due to a lack of, or insufficient, clinical data on the subject device
- Justifying that clinical data is not appropriate since the device's clinical benefit is limited to patient management or public health
- Manufacturer's justification often relies on use of usability data to support safety and performance, in lieu of clinically relevant endpoints

- Notably in the case of accessories and surgical instruments, the manufacturer states that the device does not have a clinically relevant purpose, and therefore does not require support from clinical data; this stance is not aligned to the definitions provided by MDR Article 2 (1) or Article 2(2) and questions the regulatory status of the product and indeed its intended clinical relevance. For example: The clinically relevant purpose of a surgical instrument intended to be used in combination with another device(s) is facilitation of procedural success; however, manufacturers often claim in error that the instrument's intended purpose is not clinically relevant.

Key Point: The justification provides the manufacturer with the opportunity to clearly and concisely demonstrate to the notified body, why they believe that the relevant safety and performance parameters can be adequately assessed by non-clinical methods alone. Considering that demonstration of safety and performance based on clinical data is one of the key underlying principles of the MDR, the justification may be subject to additional scrutiny and thus should clearly address each of the criteria discussed above.

Common Deficiencies in Clinical Evaluation

- A manufacturer applies Article 61(10) but also includes a body of clinical data in the clinical evaluation.
    - As discussed previously, once demonstration of conformity is based on clinical data, Article 61(10) is no longer applicable. Article 61(10) is only applicable in cases where conformity can be adequately confirmed using non-clinical data alone.
        - For some devices, a limited amount of clinical data may be identified by the manufacturer. For example, low quality PMS data such as complaints and vigilance, or the results of a clinical investigation on a novel surgical technique where the instruments have been sterilized by the device under evaluation. Whilst this data can be included in the clinical evaluation, it clearly does not add any tangible value to the demonstration of the device's conformity with the GSPRs and Article 61(10) remains applicable.
        - In other cases, for example a surgical instrument specifically intended to be used in conjunction with an implant system, procedure level clinical data such as procedure success and intraoperative complications may provide an indirect, but valuable, indicator of safety and performance of the instrument itself. In this scenario, article 61(10) would not be considered applicable.
- CER does not include a discussion of the relevant non-clinical testing or demonstrate how it supports conformity to at least Annex I, GSPR 1 and 8
    - A detailed discussion of the relevant non-clinical testing is not expected here. Rather the manufacturer should provide a summary of the data, clearly demonstrating how this data validates the safety and performance parameters determined from the state of the art
- Manufacturer states that the device does not provide any clinical benefit, meaning that it is impossible to perform any sort of benefit-risk analysis
    - All medical devices and accessories to medical devices are expected to provide a clinical benefit, otherwise it raises the question as to whether they fall under the scope of MDR or not. In the absence of a defined clinical benefit, it is not possible to conduct a meaningful

benefit-risk analysis. Often, the clinical evaluation contains contradictory statements such as the device does not provide a clinical benefit however the clinical evaluation concludes that the benefits of using the device outweigh the residual risks.

- Determination of clinical benefits can be challenging for accessories to medical devices. However, manufacturers are advised to consider so-called "indirect benefits" such as facilitation of a therapeutic or diagnostic intervention.

- The manufacturer does not consider "implicit claims"
  - Implicit claims are not explicitly stated by the manufacturer but are inherent to the device's intended purpose, its generic device group, or are required by the generally acknowledged state-of-the-art and must also be considered within the clinical evaluation.
- The manufacturer does not revisit the continued adequacy and applicability of their justification for deeming that clinical data is not appropriate during the certification period.
  - Changes to the continued acceptability of Article 61(10) may arise due to availability of new or unexpected clinical data on the device itself and/or on similar or equivalent devices, or if there is a change in the state-of-the-art. In such cases, while clinical data may not have been appropriate initially, the manufacturer may need to adjust and update the clinical evaluation and consider if Article 61(1) may be more applicable. On the other hand, it is very unlikely that a device initially evaluated by clinical data would fall into Article 61(10) at a later stage. Exceptions may include if all explicit clinical claims have been removed and no implicit clinical claims exist.

Common Deficiencies in Post Market Surveillance Including Post Market Clinical Follow-Up:

- PMS plan is not provided and/or general PMCF activities are not planned
- Once marketed, the manufacturer intends to collect clinical data via specific PMCF– no rationale for this approach is provided

Key Point: The MDR requires a manufacturer to monitor safety and performance of all devices once placed on the market in accordance with the PMS plan per Annex III. While these PMS activities are generally applicable to devices that do and do not follow the Article 61(10) approach, expectations regarding PMCF activities are usually different between these two groups of devices, as discussed below.

General PMCF activities as defined by Annex XIV, Part B, Section 6.2 (i.e., literature search, user feedback) are expected to continue to support the manufacturers' justification that clinical data is not appropriate for these devices. It may be possible to address these activities within the PMS plan; however, it must be clear what activities are considered reactive data collection versus general PMCF.

Collection of clinical data via specific PMCF activities as defined by Annex XIV, Part B, Section 6.2 (b) suggests that clinical data is indeed appropriate to demonstrate safety and performance and is generally not considered conducive to an Article 61(10) approach. It is recommended that manufacturers engage in structured dialogue with their notified body to discuss acceptability of their proposed strategy