The European Association of Medical devices Notified Bodies

Team-NB Position Paper

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Orphan In-vitro diagnostics medical devices

INTRODUCTION & SCOPE

The proposed amendments and revisions to the current EU pharmaceutical legislation, including Regulation (EC) 141/2000, aim to enhance patient access to high-quality medicinal products and address unmet medical needs within the European Union[1]. However orphan medical devices (MD and IVD), which play a crucial role in patient care for rare clinical conditions and associated unmet medical needs, appear to be overlooked. There are also no specific provisions for Orphan MD or IVD devices in Regulation (EU) 2017/745 and Regulation (EU) 2017/746 respectively. In June 2024, the "MDCG guidance 2024-10 Clinical evaluation of orphan medical devices" was published to provide criteria for defining orphan medical device status and their assessment, particularly regarding the clinical evaluation of these devices. Nevertheless, provisions for orphan IVD devices remain absent. Given their unique challenges, and in the absence of specific provisions in the IVDR, the application of IVDR requirements to orphan devices should be balanced and proportionate in light of Article 35 of the Charter of Fundamental Rights, so that the pre-market clinical evidence requirements are sufficiently met without unduly hindering or delaying patient access to these important devices. The purpose of this position paper is to provide notified body views on what could be orphan IVD definition criteria and how Orphan IVD's could be assessed to successfully achieve CE marking for providing necessary diagnostic measures for rare clinical conditions.

This document aims to provide viewpoints of notified bodies to manufacturers, the European Commission, the MDCG and other relevant stakeholders notified bodies on the conformity assessment and performance evaluation aspects pursuant to the IVDR of IVD medical devices, including software and accessories for those devices that qualify as 'orphan devices' (OD) or that have an orphan indication, within the meaning of this position paper. This position paper is relevant to devices across all risk classes as per the classification rules defined in the IVDR. In-house manufactured devices as per Art. 5.5 of the IVDR, Laboratory Developed Tests, as defined by the FDA, and RUO devices are outside the scope of this position paper.

I - GENERAL CONSIDERATIONS

[1] COM_COM(2023)0193_EN.pdf (europa.eu), accessed last: 9th January 2024

1. Orphan device status and indications

As previously stated, the IVDR does not provide a definition for orphan IVD devices, nor does any other European regulatory framework. **MDCG 2024-10** "Clinical evaluation of orphan medical devices" defines orphan medical devices (excluding IVDs) as:

"*devices specifically intended to benefit patients in the treatment, diagnosis, or prevention of a disease or condition that presents in not more than 12,000 individuals in the European Union per year; and meeting at least one of the following criteria:*

- *there is insufficiency of available alternative options for the treatment, diagnosis, or prevention of this disease/condition, or*
- *the device will offer an option that will provide an expected clinical benefit compared to available alternatives or state of the art for the treatment, diagnosis, or prevention of this disease/condition, taking into account both device and patient population specific factors*."

This definition extrapolates the number of affected individuals for orphan medical devices (excluding IVDs) from the FDA Humanitarian Use Device (HUD) designation and calculates on the basis of an EU population of 447 million people.[2] While following US methodology, this approach does not consider the EU definitions for rare diseases, as introduced in Regulation (EC) 141/2000 on orphan medicinal products: *"(…) a prevalence of not more than five affected persons per 10,000 (…) while it can be considered for (…) life-threatening, seriously debilitating or serious and chronic condition (…) even when the prevalence is higher than five per 10,000".* [3]

Notified bodies acknowledge the challenge to correctly estimate the general burden of rare diseases and rare clinical conditions[4], and even more so the number of devices needed to diagnose and treat individual rare diseases or conditions. However, regulatory and policy guidance often require certain epidemiological estimates. Taking into consideration approaches by countries like the USA and Japan, that have established not only orphan device definitions before the EU, but also introduced special programs for orphan device assessment and/or designation, while similarly incorporating the existing EU rare disease definition, notified bodies consider the following definition for orphan IVD devices, to be appropriate:

"An orphan in-vitro diagnostic device, falling under the scope of the Regulation (EU) 2017/746, is intended to provide medical information to benefit patients in the treatment, diagnosis, or prevention of diseases or certain clinical conditions present in not more than 1 in 2000 people (prevalence) in the European Union"

Under the condition that:

There is no appropriate alternative device or option for treatment, diagnosis, or prevention of this disease/condition, or the device will offer an option that will provide an additional expected clinical benefit

[2] https://health.ec.europa.eu/MDCG 2024-10
[3] EUR-Lex - 02000R0141-20190726 - EN - EUR-Lex (europa.eu), accessed last: 12th June 2026
[4] Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database | European Journal of Human Genetics (nature.com), accessed last: 12th June 2026

compared to available alternatives or state of the art for the treatment, diagnosis, or prevention of this disease/condition, taking into account both device and patient population specific factors."

Note: In the case of new diseases or variants, the incidence of a disease or condition may also be relevant to determine the orphan device status, per MDCG 2024-10.

2. Qualification of Orphan IVD's / justification of Orphan IVD indication

A manufacturer who claims that his device is an Orphan IVD should provide specific information that supports the OD status or OD claim/indication. This information should be included in any documentation submitted to a notified body or an expert panel for the purpose of determining the OD status and, eventually, in the Performance Evaluation Report (PER). The information justifying the OD status should be based on scientific rationale addressing at least epidemiological and device-related considerations (see non-exhaustive guiding principles below). It is to be distinguished from the clinical evidence that is required for the purpose of conformity assessment of the orphan IVD. Manufacturers and notified bodies may seek advice from the expert panels on the OD status or specific questions related to OD status once the panel is operational.

The manufacturer should provide a description of the device, its intended purpose, and a scientific rationale for why the proposed intended use is considered necessary or important in the context of the management of the orphan population (or orphan subpopulation) in question, with reference to device-specific factors. If relevant, the manufacturer may choose to describe a specific indication for use in addition to, to assist in providing this justification. The device description should include a description of the current state of the art and alternative therapies (if any, including the relative availability of alternatives) to justify the relevance of the intended use or indication.

II - CONSIDERATIONS FOR PERFORMANCE EVALUATION OF ORPHAN IVD'S

Regulation (EU) 2017/746 IVDR puts higher emphasis on the clinical evidence evaluation including clinical benefit-risk analysis by presenting sufficient scientific and clinical data, which are usually limited for rare diseases and conditions. Having regard to the challenges to generate clinical data in the premarket phase, Orphan IVD's may be granted market access with acceptable limitations in the amount and quality of pre-market clinical data, provided that appropriate measures are implemented in the post market stage. There must be sufficient clinical evidence to demonstrate an expected clinical benefit, and that the device performs as intended with an acceptable level of safety. To address and resolve any limitations in pre-market clinical evidence as soon as possible, an adequate PMPF plan must be developed and evaluated by Notified Bodies, to ensure appropriate collection and generation of post-market clinical data.

The requirements for the performance evaluation of medical devices laid down in Chapter VI, and Annex XIII, Annex XIV of the IVDR also apply to Orphan IVD's. In alignment with MDCG-2024-10, section 5, orphan IVD's may be granted market access with acceptable limitations in the amount and quality of pre-market clinical data, provided that appropriate measures are implemented under the following provisions:

- Relevant GSPRs must be identified, where the manufacturer specifies and justifies the level of clinical evidence necessary for demonstrating conformity with those relevant GSPRs, taking into consideration the characteristics of the device and its intended purpose;
- existing non-clinical and limited clinical data is sufficient to demonstrate that the relevant GSPRs in Annex I IVDR are met, that the benefit-risk ratio is acceptable, and that it is expected that the device will provide a clinical benefit taking into account the clinical condition, the state of the art, and the safety of patients.

Additional aspects that should be taken into account when collecting and reviewing clinical evidence:

- Expert medical opinions might serve as additional input for state of the art description, e.g., from relevant medical societies, health care agencies, European Reference Networks for rare and complex diseases.
- Clear specification and confirmation of the specific clinical benefit and medical need of the device or device family in the treatment or diagnosis of the orphan disease(s) in question, also considering all current alternative treatment options.
- It must be acknowledged that at times state of the art might be very limited, however an expert opinion giving sufficient specifics on the clinical need and non-availability of diagnostics can be acceptable
- The PEP and all relevant performance reports (SVR, APR, CPR, PER) should address specific elements connected to the Orphan IVD status and the justification/rationale thereof; I.e. rare disease/clinical condition specific considerations, epidemiology, specifics on patient population, severity of the disease / clinical condition, challenges in obtaining pre-market data, specifics on sample sizes and limitations if applicable, international market analysis (e.g., device or similar claims available in other regulatory jurisdictions, appropriateness thereof for EU market)
- The Orphan IVD status should be clearly stated in the IFU and SSP (if applicable). In the SSP, the OD status should be explained in lay user language, if applicable.

1. Clinical Evidence

1.1. Non-clinical performance data sources

During performance evaluation assessment, notified bodies consider accepting a greater variety of data sources to demonstrate clinical evidence, also including non-clinical data (as specified in MDCG-2024-10, section 6). Non-clinical performance data can have a supportive role in establishing what the acceptable safety, performance and benefit-risk profile of the device will be. The use of these data should be duly justified by providing clear explanation on their relevance with regard to the orphan device.

Non-clinical performance data may include for instance (non -exhaustive list):

- *in silico* predictions,
- data modelling,
- (AI) simulations,
- organoid/microfluidic systems,
- 2D/3D tissue models,
- appropriate data from *ex vivo* models and cadaveric studies,

- Information with regard to the state of the art of the technology.
  The appropriateness of the sources of data will be assessed by the notified body on a case-by-case basis.

1.2. Clinical performance data sources

Clinical evaluation of orphan devices requires appropriate identification of relevant clinical data, appraisal of the quality and scientific validity of each data source, and analysis of the results and conclusions of these data sources.

1.2.1. Data from legacy IVDs

We acknowledge that a substantial group of Orphan IVD's also qualify as legacy devices that were previously placed on the EU market under the IVDD. In the case of legacy orphan IVD device, data from post-market surveillance and vigilance (PMSV) should be available to support the claimed performance of the device. The situation will be more complex for novel orphan IVD where PMSV will not be available.

Using clinical performance data sourced from IVDD performance and clinical performance studies may be acceptable, as outlined in the MDCG 2022-02. This can include data from prior use under the IVDD, such as PMPF data, PMS safety data, retrospective studies of registry data, data from previous independent research, etc. provided that the data sourced from legacy devices can be applied to the orphan IVD device claim or indication. Legacy data shall be accompanied by at least one further source of clinical performance data as defined in the IVDR and specified in the MDCG-2022-02. There may be exceptions where it may be justifiable to generate some or all new clinical performance data in the post-market phase following IVDR CE-marking.

1.2.2. Data from off-label use

Manufacturers may consider the usage of off-label data from CE-marked IVDs to be used as clinical evidence for (legacy) orphan IVD certification, if device has been systematically used off-label for an orphan indication by the clinical community across the EU/world for many years, to the extent that it is now considered by clinical experts as part of best clinical practice for the management of that disease or condition.*

- In certain cases, it might be acceptable to consider clinical data from off-label use when considering revision or expansion of a device's intended purpose to include this use/indication, instead of conducting a clinical investigation/clinical performance study, provided that:

  - the decision to not perform a clinical investigation is justified and compliant with relevant IVDR requirements;
  - the off-label clinical data is of sufficient amount and quality to allow clinical evaluation and notified body assessment; and
  - the PMPF plan sufficiently justifies how the limitations in clinical data will be addressed through PMPF activities.

*Off-label data can be considered "clinical data" under Regulation (EU) 2017/745, §2, definition 48 – IVDR has no definition for clinical data, thus does not negate this usage

Note: In exceptional cases, RUO data could be used as supplemental data to support clinical evidence, but decisions shall not be based exclusively on RUO data.

1.2.3. Pre-market clinical performance data

Clinical investigations of orphan device can be challenging to perform due to the limited numbers of affected subjects, the scarcity of the available data and resources. When designing a clinical investigation for Orphan IVD's, involvement of appropriate clinical experts should be sought to ensure the study is appropriately designed to reflect the clinical needs of the target population. In addition, engagement with patients, patient associations of the target population may also be helpful in confirming whether the study includes patient-relevant clinical outcomes.

Note: For clinical evaluation of orphan indications, it may be appropriate to avail of clinical data extrapolated from the use of the device in other, non-orphan populations.

The following considerations may be taken into account when generating and evaluating pre-market clinical performance data for orphan IVDs or orphan IVD indications:

- Clinical investigations and evidence generation shall consider collaboration with multiple centres where appropriate and proportionate to ensure sufficient patient participation and to enhance the potential for generalisability of results (see also MDCG-2024-10, Section 8).
- Usage of other post-market clinical evidence and post-market surveillance, in alignment with MDCG-2024-10, section 9.4: post-market setting, clinical data can be collected from sources other than through PMPF clinical investigations. These sources are often referred to as 'real world data' and can be used to generate 'real world evidence'. This clinical data is collected in the post-market setting (e.g., during PMS or certain PMPF activities like registries), during the routine use of the device in clinical practice. As with all devices, manufacturers of orphan devices must have an appropriate PMS system in place.
- Clear description of clinical risks and assessment of clinical benefit-risk for the device in question (at times a high level of uncertainty and clinical risk might be acceptable in relation to the respective clinical benefit-risk – this however, needs to be discussed in great detail and be supported by expert opinions)
- Opinions/advice from a patient-network or patient-representative-initiatives. Make use of (1) patient registries/reference network registries[5] for real-world evidence (RWE) and (2) other central databases or modules**
- Consider devices and respective "reliance data" derived thereof from devices for rare diseases or clinical conditions with similar intended use/indications that are registered in other regulatory jurisdictions that have a similar regulatory oversight e.g., U.S.; Japan; Switzerland, UK as sources for decision making

** Orphan device registration in a specific module in EUDAMED or including a specific Orphan identifier would increase the traceability of Orphan IVDs using interoperable data and data formats (ICD-11, SNOWMED, ICD-10,

[5] Frontiers | Rare Disease Registries Are Key to Evidence-Based Personalized Medicine: Highlighting the European Experience (frontiersin.org), accessed last: 12th June 2026

FHIR). See similar approach for orphan medicinal products: EC Union/Community Register of Orphan Medicinal Products[6]

Manufacturer may furthermore consider leveraging retrospective data in supporting clinical evidence claims for Orphan IVD's. This may include, but is not limited to:

- Retrospective data analysis from registries
- Case studies and reports, with limited patient numbers might serve as an additional clinical performance data input
- Appropriate marketing and sales data from IVDD self-declared devices
- Appropriate performance evidence from in-house manufactured IVDs

Clinical investigations and evidence generation shall consider collaboration with multiple centres where appropriate and proportionate to ensure sufficient patient participation and to enhance the potential for generalisability of results, as stated in MDCG-2024-10, Section 8.

Note: For clinical evaluation of orphan indications, it may be appropriate to avail of clinical data extrapolated from the use of the device in other, non-orphan populations.

1.2.4. Post-market clinical performance data and surveillance

Limitations in pre-market clinical data make the post-market surveillance and follow-up highly important for the life-cycle evaluation of Orphan IVD's. If pre-market limitations in clinical performance data have been identified and deemed acceptable, it is important that these limitations will be addressed in well-defined and structured PMCF activities considering clinical benefit/risk. The following provisions may be taken into account:

- Well-structured PMPF/PMS plan, detailing the pre-market limitations in clinical performance or clinical evidence that have been identified and how these limitations will be addressed and in what time period, e.g.,
  - Include plans for prospective performance studies and conduction thereof in PMPF
  - Include plans for retrospective data analysis available from registries
  - PMPF Plans and resulting PMPF activities should focus on the gathering of additional data to be obtained from patients with the (confirmed) rare condition or disease, that is claimed in the related documentation (IFU, SSP) and intended purpose. This is done to further substantiate the performance claims. In addition, any newly obtained evidence that could shadow doubts about the claims made, need to be considered.
- Prospective data collection by manufacturer through follow up of every device sold after marketing as integral part of PMPF IVDR Annex XIII (Part B), e.g., by clinical performance studies or mandatory use of registries for every device sold and EUDAMED registration (the latter shall be performed as soon as available)

[6] Union Register of medicinal products - Public health - European Commission (europa.eu), accessed last: 12th June 2026

- Installation of appropriate reporting/update intervals to NB for the manufacturer additionally to PSUR/PMSR Article 81/80 for e.g., certificates with conditions if appropriate
- Mandatory use of registries for every device and EUDAMED registration to allow follow-up, the latter shall be performed as soon as available
- Clear instructions to users on how to report incidents, complaints or other experience to the manufacturer in e.g. the IFU, SSP

It should be ensured and verified that the PMPF plan is implemented and followed to completion. Limitations in pre-market clinical evidence and the Orphan IVD status shall be clearly stated in the IFU and SSP. In the SSP, the OD status should be explained in lay user language, if applicable.

Additionally, notified bodies may use the option as specified in in IVDR Annex VII, 4.8 and in alignment with MDCG-2022-17 as well as MDCG-2024-10, section 10.2, to grant conditional certification to Orphan IVD's when pre-market clinical performance or clinical evidence is limited, and gaps will be needed to address/confirm by PMS/PMPF activities. Here issuing certificated with specific conditions or provisions may come into play.

III - PROCEDURAL CONSIDERATIONS FOR ORPHAN IVD'S

1. Notified body activities prior to certification

The OD status of the device should be checked by the notified body as early as possible, for example as part of structured dialogue before or during initial conformity assessment activities. This should be based on the justification and information provided by the manufacturer; in case where there isn't sufficient information to decide on the OD status, the notified body or the manufacturer should consult the expert panel for advice (in alignment with MDCG-2024-10, Part B section 10), for more details see chapter III – 4. of this document.

Role, activities and scope of an orphan device specific expert panel are currently being discussed in the draft act intending to amend Implementing Decision (EU) 2019/1396 for Implementation of device expert panels/boards at EMA for rare diseases & paediatric cohorts.

2. Notified body certification activities of IVD's with an Orphan device status

The OD status will be reviewed by the notified body, as part of the application review process, before reviewing and accepting the technical documentation. When the orphan device status is established and confirmed, the technical documentation should be assessed following the same principles as for IVD medical devices that do not have an OD status. However, when assessing the manufacturer's Performance Evaluation Plan (PEP) and Performance Evaluation Report (PER), the product reviewers/clinical experts will consider the specific aspects addressed in this position paper, including the acceptability of limited pre-market clinical performance data and appropriate PMPF activities to generate additional post-market clinical performance data. The notified body's assessment of the PER should address the information supporting the orphan device status and, where applicable, the rationale for accepting limitations in the

pre-market clinical performance data and the activities proposed by the manufacturer in its PMS plan and PMPF plan to obtain the necessary additional clinical performance data. The possibility for notified bodies to issue certificates with conditions can contribute to increasing the necessary flexibility to apply the reinforced clinical evidence requirements to devices that have a demonstrable track record of safety.

3. Notified body certification activities after initial certification

The notified body will consider PMS data, in particular the main findings from PMPF as part of the agreed surveillance activities and PSUR/PMSR evaluation pursuant to IVDR Article 81/80 and verify whether the device's benefit-risk profile continues to support the placing of the device on the market. As part of their surveillance activities and post-certification monitoring, notified bodies will monitor compliance with any conditions/provisions that are binding for the manufacturer and associated with the certification decision, such as updates to clinical data at defined intervals. Where applicable, especially if listed as part of the conditions for certification, the notified body also needs to review the performance evaluation that the manufacturer has updated based on its PMS Plan and PMPF Plan.

When the conditions/provisions on the certificates are not fulfilled/met by the manufacturer, the notified body will consider the impact thereof on the certificate's validity, as specified in their procedures. Not fulfilling the conditions/provisions ultimately will lead to suspension or withdrawal of the certificate.

4. Role of the expert panel

While it rests with the manufacturer to demonstrate that its device meets the criteria for orphan device status, the expert panels established in accordance with MDR Article 106 and IVDR Annex IX 4.9 may be requested to provide advice on the orphan device status and the clinical data needed for the clinical evaluation. The consultation of an expert panel in relation to an orphan device described in this section is optional and independent of the performance evaluation consultation procedure (PECP) provided for in IVDR. Advice from the expert panel will be however considered during the notified body's conformity assessment activities and reports.

The current draft act intending to amend Implementing Decision (EU) 2019/1396 for Implementation of device expert panels/boards at EMA for rare diseases & paediatric cohorts, supports the here described and proposed proceedings, for different scenarios of expert panel consultations.

a. The orphan device status will influence the expected level of pre-market clinical evidence, notably the justification for limitations in the pre-market clinical evidence and an acceptable level of pre-market clinical uncertainty. It is therefore recommended that manufacturers of devices that may qualify as Orphan IVD consult an expert panel on their intended clinical development strategy early in the process. The expert panel may, as a necessary first step, assess the manufacturer's justification regarding the orphan device status. In a second step, the expert panel may review the manufacturer's intended clinical development strategy and proposals for clinical investigation. This scenario might be particular applicable to newly developed Orphan IVDs.
b. When a manufacturer plans to submit a device for conformity assessment at a notified body, where the device has an Orphan device status, the manufacturer is encouraged to get in contact with a notified body early on, e.g., through a structured dialogue. During this the manufacturer and the notified body can

discuss the orphan status and agree for an expert panel advice, if deemed necessary by at least one of the two parties.

c. A notified body involved in the conformity assessment of a device for which the manufacturer claims an orphan device status may seek advice from an expert panel, if deemed applicable, i.e. regarding the Orphan IVD status or clinical evidence demonstration including any justification provided by the manufacturer regarding limited clinical data, the acceptability of clinical uncertainty and proposed post-market clinical follow-up activities. Before submitting such a request, the notified body should consult the manufacturer and where appropriate give the manufacturer the opportunity to provide input into the request. For that purpose, the notified body should put forward specific questions for which it seeks the panel's advice.

5. IVD specific aspects in relation to Orphan Device status

5.1. In-house manufactured devices and laboratory developed tests

In-house manufactured devices (as per Article 5 (5)) and Laboratory Developed Tests (as defined by the FDA) are outside the scope of this position paper, as these are devices that are not put forward in the conformity assessment of IVD medical devices by a notified body, per IVDR. That said, the notified body can onboard clinical performance data and evaluate clinical evidence that originates from these devices, when there is a clear relationship with device under review that has an IVD OD status; for example, when the Orphan IVD previously was used as an in-house manufactured test or a laboratory developed test. Especially when the availability of clinical samples is (very) limited and options to obtain clinical performance data through the use of an extensive clinical performance study are limited.

5.2. Multiplex Assays

When an analyte or test with an IVD OD status is part of a multiplex device that undergoes a conformity assessment that does not have an IVD OD status, the clinical data and evidence requirements that represent the analyte or test with an IVD OD status should not be taken onboard for the remainder of the device that does not have an IVD OD status. A position paper on the assessment of multiplex IVD devices is available on the Team-NB page; a more detailed approach is currently being developed.

Conclusions

Orphan IVDs plays a critical role in the diagnosis and management of rare diseases and conditions. However, the collection and evaluation of performance data for these devices present significant challenges due to limited patient populations and data availability. The approach outlined in this position paper supports the successful completion of the conformity assessment process by leveraging existing tools within the IVDR framework—such as the option to consult expert panels and obtain certification under defined conditions.