MDCG 2026-6

Clinical evidence for orphan *in vitro* diagnostic medical devices

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1. Abbreviations and terminology

For the purposes of this guidance document, the below terms are defined as follows:

- Analytical performance	IVDR Article 2(40)
- Benefit-risk determination	IVDR Article 2(17)
- Clinical benefit	IVDR Article 2(37)
- Clinical evaluation	Term in this document that refers to the evaluation of clinical performance that is conducted as part of the performance evaluation process.
- Clinical evidence	IVDR Article 2(36)
- Clinical performance	IVDR Article 2(41)
- EMA	European Medicines Agency
- GSPR	General Safety and Performance Requirements - IVDR Annex I
- IFU	Instructions For Use
- In-house IVD	An IVD that is manufactured and used only within a health institution established in the Union and that meets all conditions set in Article 5(5) of the IVDR (per MDCG 2023-1)
- Intended purpose	IVDR Article 2(12)
- IVD	*In vitro* diagnostic medical device
- IVDR	*In Vitro* Diagnostic Medical Devices Regulation, referring to Regulation (EU) 2017/746
- MDCG	Medical Device Coordination Group
- Non-clinical data	Any relevant data that does not meet the IVDR definition of data on clinical performance
- Non-orphan	Refers to an IVD, indication, or (sub)population which does not meet the definition of 'orphan IVD', 'orphan indication', or 'orphan (sub)population', respectively
- Orphan indication	As described in section 4.3 of this document
- Orphan IVD	As described in section 4.1 of this document
- Orphan population	As described in section 4.2.1 of this document
- Orphan subpopulation	As described in section 4.2.1 of this document
- PECP	Performance Evaluation Consultation Procedure - IVDR Article 48(6)
- PER	Performance Evaluation Report
- Performance of a device	IVDR Article 2(39)
- Performance evaluation	IVDR Article 2(44)
- PMPF	Post-Market Performance Follow-up - IVDR Annex XIII, Part B
- PMS	Post-Market Surveillance - IVDR Article 2(63)
- Target population	Group of individuals for which the IVD is intended

2. Introduction

The IVD Regulation (IVDR, Regulation (EU) 2017/746) requires that the level of clinical evidence for an IVD is sufficient to demonstrate its performance and safety before being placed on the market. This may present a challenge for IVDs that are specifically intended for use in **rare diseases/conditions (e.g. a genetic test for a rare disease) or circumstances (e.g. a toxicological test for an uncommon intoxication)**. Such IVDs are termed 'orphan IVDs' in this guidance and the criteria that they should meet in order to qualify as orphan IVDs are provided.

The necessary clinical evidence for an IVD should be based on a sufficient amount and quality of data in order to allow a qualified assessment of its safety, performance, and the intended clinical benefit(s). IVD performance is demonstrated by substantiating scientific validity, analytical performance, and clinical performance. For orphan IVDs, which by their nature address very small patient populations, generating clinical performance data within a reasonable timeframe may be challenging due to limited specimen availability.

The field of rare disease/condition/circumstance diagnostics evolves rapidly, with technological developments that sit on the edge between research and clinical diagnostics. Additionally, low sales volumes may limit the commercial viability of orphan IVDs on the EU market. It is thus not surprising that many orphan IVDs are manufactured in-house by health institutions. These health institutions may face similar challenges as IVD manufacturers when generating clinical evidence for their in-house orphan IVDs.

Given their unique challenges, the application of IVDR requirements to orphan IVDs should be balanced and proportionate, so that clinical evidence requirements are sufficiently met without unduly hindering or delaying the clinical use of these important devices. There are circumstances where it is acceptable for orphan IVDs to be placed on the market, or to be manufactured and used in-house, with limitations in clinical performance data. Without dedicated guidance, manufacturers, notified bodies, health institutions and regulators may interpret the clinical evidence requirements differently for these IVDs.

Some IVDs may have both 'orphan' and 'non-orphan' indications. Where sufficient clinical evidence for the orphan indication is difficult to demonstrate, the principles in this guidance may be applied to support the orphan indication only.

This guidance is divided into two main parts:

PART A – Clinical evidence considerations (applicable to both manufacturers and health institutions):

- The acceptability of limitations in pre-market clinical performance data for orphan IVDs
- Key considerations on the evaluation of clinical performance of orphan IVDs
- Generating post-market clinical performance data for orphan IVDs

PART B – Procedural considerations (not applicable to health institutions):

- Guidance for notified bodies on the assessment of orphan IVDs
- The role of the expert panels in the context of orphan IVDs

Annexes:

1. Examples of orphan IVDs
2. Orphan IVD-specific factors to include in the performance evaluation report
3. Extrapolation of clinical performance data to orphan indications
4. Considerations for clinical performance studies with orphan IVDs

3. Scope

This document provides guidance to manufacturers, notified bodies, expert panels, health institutions, and regulators on the clinical evidence requirements for orphan IVDs and for IVDs that have an orphan indication within the meaning of this guidance. The guidance is relevant to IVDs across all risk classes. Particular attention is given to the clinical performance of orphan IVDs, which forms part of the clinical evidence and performance evaluation requirements stated in IVDR Chapter VI. Where relevant, the guidance should be read in conjunction with other MDCG guidance documents, in particular MDCG 2022-2 on general principles of clinical evidence for IVDs.

Note to EU health institutions that manufacture orphan IVDs in-house

This document gives guidance on the clinical evidence for orphan IVDs, including performance data to demonstrate conformity with the General Safety and Performance Requirements (GSPR) of IVDR Annex I. IVDs manufactured and used within EU health institutions in accordance with IVDR Article 5(5), termed 'in-house IVDs', are exempted from most of the requirements of the IVDR, including certification. However, in-house IVDs must meet the relevant GSPR of Annex I. In addition, the IVDR provisions on performance studies can also apply to studies with in-house IVDs[1]. Therefore, **the general principles[2] outlined in sections 4 to 9 and in annexes 3 and 4** of this guidance are relevant to health institutions when manufacturing in-house orphan IVDs, provided the criteria and conditions set forth in this document are fulfilled. When demonstrating compliance with the relevant GSPR, claims made about the orphan status of an in-house IVD should be sufficiently substantiated and documented. Health institutions should read this guidance in conjunction with the MDCG 2023-1 guidance on the health institution exemption under Article 5(5).

[1] See question 9 in MDCG 2025-5.

[2] These 'general principles' refer to means to demonstrate conformity of in-house orphan IVDs with the GSPR, i.e. before the clinical use of the in-house IVD. They cover the determination of the orphan status, the important role of non-clinical data, the generation of clinical performance data and the acceptability of limitations in such data. They also refer to the approach of obtaining extra clinical performance data after putting the in-house orphan IVD into service. In addition, health institutions can also use the principle of extrapolating performance data available from a non-orphan population to orphan indications, as described in Annex 3.
Specific statements related to notified bodies, certification, CE marking, reports and expert panels are not applicable to orphan IVDs manufactured by health institutions.

4. Orphan IVD status and orphan indication

4.1. Orphan IVD criteria

For the purpose of this guidance, an IVD is regarded as 'orphan IVD' if it meets the following criteria:

- the IVD is specifically intended to test persons for a disease/condition or in circumstances that present in not more than 12,000 individuals in the European Union per year[3], **AND** at least one of the following criteria are met:
    - there are insufficient available alternatives, or
    - the IVD will provide an expected clinical benefit compared to available alternatives or state of the art.

Orphan IVDs intended to identify affected individuals can evidently be used on more persons than the actual patient population, since in the context of screening or diagnosis, not all tested individuals are affected. Also, an orphan IVD can be intended for repeat or multiple use on the same patient on a regular basis. It is therefore important to note that the epidemiological criterion above is based on epidemiological data related to incidence of the disease/condition or of the specific circumstance, not on the total number of tests performed each year. Examples of sources of epidemiological data are European Reference Networks registries, EMA records, Orphanet data etc. Annex 1 provides some examples of orphan IVDs.

It is important to note that the status as a CE-marked orphan IVD does not confer market exclusivity for that IVD. For the sustainable development of orphan IVDs, the criteria should not be interpreted so as to prevent the marketing of more than one CE-marked orphan IVD intended for use in the same disease/condition or circumstances.

4.2 Justification of orphan IVD status

A manufacturer who claims that an IVD is an orphan IVD should provide information that supports the orphan status. The information should be included in any documentation submitted to a notified body or to the expert panels (see sections 10 and 11 and Annex 2).

The information justifying the orphan IVD status should be based on scientific rationale addressing at least epidemiological and IVD-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.

Manufacturers and notified bodies may seek advice from the expert panels on the orphan status (see section 11).

[3] Extrapolated from the population estimate criteria for Humanitarian Use Device (HUD) designation established by the U.S. Food and Drug Administration (FDA) and calculated on the basis of an EU population of 447 million, see www.fda.gov/regulatory-information/search-fda-guidance-documents/humanitarian-use-device-hud-designations.

4.2.1 Epidemiology of the disease/condition/circumstance

The manufacturer should provide a description of the specific disease/condition, or of the specific test circumstance, that is present in not more than 12,000 individuals in the EU per year (hereafter referred to as the '**orphan population**') for which the orphan IVD is intended to be used.

The manufacturer may also justify that the IVD is intended to test individuals for a disease/condition/circumstance that presents in a clinically valid patient subpopulation (not more than 12,000 individuals in the EU per year and hereafter referred to as an '**orphan subpopulation**') within a disease/condition/circumstance with an annual incidence of more than 12,000 in the EU.

The manufacturer should provide documentation with population incidence estimates in order to support the epidemiological criterion. Authoritative references (e.g. from peer-reviewed medical literature and/or public health statistics) relevant to the EU population should be provided where available. It is acknowledged that such documentation will be limited in some cases. Additional supporting data for incidence estimates may be included, e.g. data from health service or national level, from other regions, from independent clinical experts or from medical society consensus statements. The orphan status may then be justified by providing an EU population incidence based on extrapolation and considering all relevant factors, including heterogeneity of the incidence in the EU and across regions.

In case the IVD is intended to test for a rare disease (defined as affecting no more than 5 in 10,000 persons in the EU[4]), **AND** where it is expected to identify/diagnose or to provide medical information for their management in not more than 12,000 such individuals per year, this can be accepted as sufficient justification of the epidemiological part of the criteria.

For orphan subpopulations, the manufacturer should provide information to justify the existence of a valid orphan subpopulation with a disease/condition/circumstance that presents in more than 12,000 individuals per year. This can include providing a scientific rationale for why the IVD is only intended for use within that subpopulation and the intended use would not be appropriate for the wider population with a non-rare disease/condition/circumstance.

Arbitrary limitations of use to only a subpopulation of patients to meet the incidence criteria will not be considered sufficient, as it could be clinically appropriate to use the same IVD and therefore generate more clinical performance data in the remaining larger population with the non-rare disease/condition/circumstance. Literature references and clinical expert statements should be provided where available to substantiate the justification.

4.2.2 Target population

The target population for the orphan IVD should be clearly defined. Significant performance challenges may be encountered if an orphan IVD is applied to the general population, in particular in the context of wide screening applications. Owing to the low prevalence of the condition within the population, appreciable levels of false positive results may be expected based on statistical factors. Defining and focusing the population to be tested can reduce the expected false positive rates and improve positive predictive values.

[4] Pursuant to the Council Recommendation of 8 June 2009 on an action in the field of rare diseases, for the purpose of Union-level policy work, a common definition of 'rare disease' as a disease affecting no more than 5 per 10,000 persons should be used.

4.2.3 IVD description, insufficiency of alternatives and expected clinical benefit

The manufacturer should provide a description of the IVD, 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 (sub)population in question. The description should include the current state of the art and the relative availability of alternatives to justify the relevance of the intended use or indication.

An explanation should be provided as to why the IVD would offer an expected clinical benefit compared to available alternatives or state of the art for the diagnosis or management of the disease/condition or for its use in rare circumstances. Information from medical literature (e.g. from clinical guidelines) or consensus statements from clinical experts or medical societies may be used to support the justification. Relevant non-clinical data on the IVD, and/or data on similar CE-marked IVDs, can support a statement that the orphan IVD will provide an expected clinical benefit.

4.3 Orphan indication

In addition to IVDs considered to have an orphan status based on the criteria described in section 4.1, it is recognised that an IVD may have a specific intended purpose for an orphan (sub)population while it also has another intended purpose in larger patient populations. In such cases, where duly justified, the principles outlined in this guidance for demonstrating sufficient clinical evidence may be applicable to these IVDs for the purposes of supporting their orphan indication only.

The manufacturer should justify that the intended purpose in the orphan (sub)population is sufficiently different to the other intended purpose, such that the clinical evidence for the non-orphan intended purpose is not applicable and there is an authentic challenge to generating clinical performance data for the orphan indication.

In the case of orphan indications, the extrapolation of (clinical) data available for the non-orphan population may be of particular relevance. The appropriateness of extrapolation largely depends on:

- similarity between the existing non-orphan and orphan (sub-)population characteristics;
- statistical considerations, i.e. how easy it is to translate evidence generated for the non-orphan to the orphan population;
- the quality of the available data in terms of study design, data collection, and measurement;
- and whether the extrapolated evidence constitutes valid scientific evidence.

Further considerations for extrapolation of data are provided in Annex 3.

PART A – Clinical Evidence Considerations

5. The acceptability of limitations in pre-market clinical performance data

Because generating pre-market clinical performance data can be challenging for orphan IVDs, market access may be granted with acceptable limitations in the amount and quality of such data, provided that appropriate measures are implemented. The required level of clinical evidence should reflect the specifics of orphan IVDs and should not necessarily be the same as for non-orphan IVDs. However, there must still be sufficient clinical evidence to demonstrate an expected clinical benefit and to establish that the device performs as intended with an acceptable level of safety. Remaining limitations should be addressed through adequate post-market performance follow-up (PMPF) and post-market surveillance (PMS) plans for timely collection of post-market clinical performance data. Limitations should be linked to those parameters which are particularly challenging for clinical performance data generation, e.g. when there is no shortage in negative specimens, sufficient testing should be performed to elaborate specificity.

As with all IVDs, orphan IVDs must meet the GSPR that are relevant to them. The manufacturer must specify and justify the level of clinical evidence necessary for demonstrating conformity with those relevant GSPR[5], taking into consideration the characteristics of the IVD and its intended purpose[6]. When specifying the level of clinical evidence necessary, important characteristics to consider include the disease/condition/circumstance, the anticipated risks, the insufficiency of alternatives and unmet medical need, and the expected clinical benefit that the orphan IVD offers, balanced against the anticipated risks.

An overall evaluation should be completed to determine and justify whether the current level of clinical evidence is sufficient for the purpose of placing the orphan IVD on the market or putting it into service. In general, a limited level of clinical performance data is acceptable if the following can be justified:

- all available data have been evaluated[7], and any limitations in clinical performance data have been identified;
- the existing data is sufficient to demonstrate that the relevant GSPR in IVDR Annex I are met, that the benefit-risk ratio is acceptable, and that it is expected that the IVD will provide a clinical benefit, taking into account the state of the art, and the safety of patients;
- it is not feasible or proportionate to generate further clinical performance data within an acceptable timeframe in the pre-market setting;
- the manufacturer has adequate PMPF and PMS plans that will timely generate data that will fully address the remaining limitations in clinical performance data as far as possible[8];

[5] I.e. for those GSPR where clinical data are needed to demonstrate conformity.
[6] Per IVDR Article 56(1)
[7] Per IVDR Annex XIII
[8] For certain orphan IVDs, residual limitations in clinical performance data may remain and can be acceptable if appropriately justified, taking into account the specific characteristics of the orphan (sub)population, the expected clinical benefit, the benefit-risk determination and the availability of alternatives.

- users of the IVD will be adequately informed of the orphan status of the IVD, of the limitations in pre-market clinical performance data, and on how to report incidents, complaints, and other clinical experience to the manufacturer. This information can be provided on the labelling, in the IFU, the summary of safety and performance (for class C and D IVDs) and/or other accompanying documentation.

While the general principles and methodology of the clinical evidence process also apply to orphan IVDs (see also MDCG 2022-2 on general principles of clinical evidence for IVDs), the following sections give granular detail on specific considerations for the clinical evidence of orphan IVDs.

6. The role of non-clinical data

'Non-clinical data' is understood as any relevant data that does not meet the IVDR definition of data on clinical performance[9]. This includes data on scientific validity and analytical performance. Non-clinical data can have a role in establishing what the acceptable safety, performance, and benefit-risk profile of the IVD will be.

All potential sources of non-clinical data should be considered for orphan IVDs. If the non-clinical data provide substantial high-quality evidence to support the safety and performance of the orphan IVD and its expected clinical benefit, this can reduce the burden of required pre-market clinical performance data and can help to justify limitations in clinical performance data that can be met through PMPF and PMS activities.

Useful sources of non-clinical data can include (non-exhaustive list):

- scientific literature and analytical performance data of similar assays;
- information with regard to the state of the art of the technology;
- datasets (e.g. registries) with previously collected information on patients' diseases/conditions/circumstances, e.g. to validate software;
- computer (*in silico*) modelling and simulations;
- data from tissue models;
- data from *ex vivo* models and cadaveric studies;
- data on contrived samples (e.g. blends containing different allelic frequencies of contrived variant constructs in background wild-type DNA for circulating tumour DNA assays) or on sample types that differ from the intended use sample (e.g. different plasma anticoagulants);
- data from similar IVDs or from research use only products.

The use of these data should be duly justified by providing a clear explanation on their relevance with regard to the orphan IVD.

[9] Per IVDR Article 2(41)

7. Clinical performance overview

The general principles of performance evaluation outlined in Article 56 and Annex XIII, Part A, Section 1 of the IVDR apply equally to orphan IVDs. The performance evaluation is a continuous, structured process. Additionally, the requirements for clinical performance studies, as set out in IVDR Articles 57 to 77 along with the provisions of Annexes XIII and XIV, also apply to orphan IVDs[10]. These requirements are further supported by the recommendations from MDCG 2022-2.

As with all IVDs, assessing clinical performance of orphan IVDs requires identifying relevant clinical performance data, appraising the quality and scientific validity of each data source, and analysing the results and conclusions of these data sources. These steps should also be followed when evaluating and justifying the applicability of existing clinical performance data for orphan IVDs, e.g. data from:

- scientific literature and expert consensus statements;
- disease registries and biobanks;
- previous clinical performance studies;
- use under a derogation from conformity assessment procedures[11];
- use of legacy devices;
- other jurisdictions where the orphan IVD has already been put into service.

Once all existing non-clinical data and clinical performance data have been evaluated, the manufacturer should be able to determine the following, regarding their device:

- which GSPR and clinical evidence requirements have been met, in total or in part, through existing non-clinical and clinical performance data;
- which requirements (if any) require additional clinical evidence to fully meet these requirements;
- what are the current limitations in clinical performance data.

By knowing the current limitations in clinical performance data, the manufacturer can generate additional clinical performance data in a focused manner, with objectives and endpoints that specifically aim to address those limitations. It may be acceptable for some limitations in clinical performance data to be addressed through specific PMPF and PMS activities.

8. Generating clinical performance data for orphan IVDs

IVDR Article 56(4) states that clinical performance studies shall be carried out unless it is duly justified to rely on other sources of clinical performance data (e.g. when a prospective clinical performance study is not possible due to the characteristics of the orphan population, it may be justifiable to rely on alternative evidence-generation approaches, in accordance with Section 7).

[10] While in-house IVDs are exempted from most of the requirements of the IVDR, provisions on performance studies can sometimes apply to studies with in-house IVDs. See question 9 in MDCG 2025-5 for more information.

[11] Per IVDR Article 54

When designing clinical performance studies for orphan IVDs, involvement of appropriate clinical experts (e.g. geneticists, epidemiologists, statisticians) should be sought to ensure the study is appropriately designed to reflect the clinical needs of the target population. The potential challenges on sample collection and sample size implications should be taken into account, in particular the difficulty to (timely) find sufficient samples from affected individuals. Efforts should be made to collaborate with multiple centres where appropriate and proportionate to ensure sufficient numbers and to enhance the potential for the generation of robust results.

Annex 4 provides further considerations that should be made when designing clinical performance studies with orphan IVDs, with particular attention to:

- defining the study population;
- selecting appropriate objectives and endpoints;
- the choice of study design and statistical approaches;
- the choice of a comparator.

For the clinical performance evaluation of orphan indications, it may be appropriate to avail of clinical performance data extrapolated from the use of the IVD in other, non-orphan populations. Considerations on the appropriate extrapolation of these data are outlined in Annex 3.

9. Post-market surveillance and post-market performance follow-up for orphan IVDs

Limitations in clinical performance data make the PMS and PMPF processes extremely important for the life-cycle evaluation of orphan IVDs.

If pre-market limitations in clinical performance data have been identified and deemed acceptable (as described previously), it is important that these limitations will be addressed through well-defined and structured PMPF activities. Therefore, for orphan IVDs, the manufacturer must have an appropriately structured and detailed PMPF plan, which is subject to notified body review. It should be ensured and verified that the PMPF plan is implemented and followed to completion; otherwise, increased reliance on post-market clinical performance data collection could undermine patient safety.

The PMPF plan should include information about:

- all identified limitations in pre-market clinical performance data, that need to be addressed;
- justification as to how the PMPF activities will address these specific limitations;
- the type of data to be generated in the post-market phase to further evaluate the clinical performance and safety of the IVD;
- how these data will be generated in an appropriate timeframe, including projections on the acquisition and the number of patient specimens that will be tested by the IVD per year, and predefined milestones on the periodic analysis of these data, where appropriate.

This may include data collected from PMPF studies, registries, or other clinical performance data and clinically relevant information in the post-market setting, including real-world data, as described below.

Depending on the limitations in pre-market clinical performance data and the reliance on PMPF to address these limitations, it may be appropriate for specific conditions or provisions (e.g. specific PMPF activities and milestones) to be defined by the notified body for the certification of these devices[12].

When developing a PMPF plan, PMPF objectives and milestones should be proportionate to the realistic availability of patients, specimens, and clinically relevant data sources. Due consideration needs to be given to the potential challenges that may be faced during execution of the PMPF plan, which may require adjustment of the expected timeframe and milestones. To this end, structured dialogue between the manufacturer and the notified body may be appropriate to discuss any challenges faced with respect to delivery of the PMPF plan.

9.1 PMPF and benefit-risk determination

The data generated from PMPF is important to enable the continued assessment of the benefit-risk profile of orphan IVDs with a higher degree of certainty. Thus, it will be important to develop a detailed risk management plan adapted to the unique characteristics of the orphan IVD, its intended use, and the limitations in pre-market clinical evidence. This plan should outline how risks will be monitored, assessed, and mitigated throughout the PMPF, and how appropriate action will be taken where these data raise new concerns regarding safety or performance.

9.2 PMPF studies

Orphan IVDs may require long-term follow-up studies to assess their performance and benefits, e.g. for some predictive or prognostic IVDs where the true clinical status will become apparent further in time. While pre-market studies may include limited follow-up periods, PMPF studies allow for continuous monitoring and evaluation over extended periods of time. The considerations outlined in Annex 4 on clinical performance studies with orphan IVDs also apply for PMPF studies and should be taken into account.

Furthermore, in addition to the general requirements and expectations for PMPF studies, particular attention should be made in the following areas:

- consider any possible condition(s)/specific provision(s) provided by the notified body in the certification and their impact on the PMPF study;
- consider how the proposed study will address any limitations in clinical evidence identified in the pre-market phase.

9.3 Other post-market clinical performance data

As with all IVDs, manufacturers of orphan IVDs must have an appropriate PMS system in place. In addition to the PMPF activities discussed above, the clinical performance data collected from PMS should be evaluated as part of the life-cycle evaluation of these devices. In the post-market setting, clinical performance data can be collected from sources other than through PMPF studies. These sources are often referred to as ‘real world data’ and can be used to generate ‘real world evidence’.

[12] See IVDR Article 51(3) and Annex VII, section 4.8.

This clinical performance data is collected during the routine use of the IVD in clinical practice. Clinical performance data from other established regulatory systems can also be relevant where EU post-market data collection remains limited due to the rarity of the orphan population, taking into account possible physiological differences between target populations.

PART B – Procedural Considerations

10. Notified body activities and responsibilities

10.1 Notified body activities prior to the certification

The orphan status of the IVD should be checked by the notified body as early as possible, for example, during the application phase before or during initial conformity assessment activities. This should be based on the justification and information provided by the manufacturer (see section 4.2) and, if applicable, advice on the orphan status provided by the expert panels (see section 11).

When the orphan IVD status is established, the technical documentation should be assessed following the same principles as for non-orphan IVDs. When reviewing the manufacturer's performance evaluation plan and performance evaluation report, the product reviewers and clinical experts should consider the aspects addressed in this guidance, including the acceptability of limited pre-market clinical performance data and appropriate PMPF and PMS activities to generate additional clinical performance data.

The notified body's assessment of the performance evaluation report 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 and PMPF plans to obtain the necessary additional clinical performance data.

10.2 Specific conditions/provisions for certification

Certificates with conditions can be used to increase flexibility for clinical evidence requirements. Orphan IVDs for which pre-market clinical performance data is deemed sufficient but needs to be further completed or confirmed through PMPF and PMS activities, are a good example where notified bodies can make use of the possibility to issue certificates with specific conditions or provisions[13]. Those may consist, for example, in requiring the manufacturer to conduct defined PMS or PMPF activities[14] within a specified period of time to generate additional clinical performance data (see section 9).

10.3 Surveillance by the notified body

As part of their surveillance activities (e.g. by evaluating post-market surveillance reports, periodic safety update reports or PMPF findings) and post-certification monitoring, notified bodies need to monitor compliance with any conditions/provisions that are binding for the manufacturer and associated with the certification decision, such as updates to clinical performance data at defined

[13] Per IVDR Annex VII section 4.8, the notified body shall have procedures in place to allow them to decide on specific milestones for further review by the notified body of the up-to-date performance evaluation (3rd indent) and to decide whether specific conditions or provisions need to be defined for the certification (4th indent).

[14] In accordance with IVDR Article 51(3), notified bodies may require manufacturers to undertake specific PMPF studies pursuant to IVDR Annex XIII, part B.

intervals[15]. 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 and its PMPF[16].

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

11. Involvement of expert panels: advice on orphan IVD status and clinical evidence

While it is the manufacturer's responsibility to demonstrate that their device meets the criteria for orphan IVD status, the expert panels[17] may be requested to provide advice on the orphan IVD status and on the data needed for the clinical performance evaluation. The consultation of the expert panel(s) in relation to an orphan IVD is optional/voluntary and independent of the performance evaluation consultation procedure (PECP)[18] (see 11.3). The notified body should give due consideration to advice provided by the expert panel and, where it does not follow such advice, it should provide duly justified reasons.

11.1 Consultation of the expert panels

The following paragraphs address different scenarios for the consultation of the expert panels, depending on the state of advancement of the IVD development or of the conformity assessment. The table below provides an overview of these scenarios.

15 See IVDR Section 4.10 of Annex VII (1st subparagraph, 1st indent).

16 See IVDR Section 4.10 of Annex VII (4th subparagraph, 1st indent).

17 Both the 'expert panel on paediatrics and rare diseases' and the 'IVD expert panel' can be involved, e.g. the former panel provides advice on the orphan status and the latter on the clinical performance evaluation. The EMA, which provides the expert panels' secretariat, determines which panel(s) will be involved. More information on expert panel support for orphan devices and on expert panels' tasks can be found on EMA's website and on the European Commission's website.

18 See IVDR Article 48(6).

Request expert panel advice		At what phase?	Remarks
When?	**By whom?**		
Early stage	**Manufacturer** See point 11.1.1	Early in the IVD development phase, i.e. prior to the clinical performance evaluation and/or study.	This early-stage advice is preferrable to the late-stage advice described in point 11.1.2(b).
Late stage	**Notified body** See point 11.1.2(a)	Early in the conformity assessment process, e.g. during the application review phase.	Particularly useful if the notified body has doubts on the claimed orphan status, the conducted clinical evaluation or the proposed PMPF and PMS activities.
	Manufacturer See point 11.1.2(b)	In an advanced or completed stage of the performance evaluation, e.g. for a legacy orphan IVD for which an application with a notified body has already been lodged.	The manufacturer should still be able to update its performance evaluation report with the expert panel's advice, i.e. before the report has been fully assessed by the notified body.

Table 1: overview of different possible scenarios for expert panel consultation

11.1.1 Early advice to manufacturers

A manufacturer of an IVD that could qualify as an orphan IVD may, prior to the clinical performance evaluation and/or study, consult the expert panel with the aim of reviewing the orphan status and, in case the orphan status is confirmed, also the intended clinical performance plan.

The expert panel will, as a necessary first step, assess the manufacturer's justification regarding the orphan device status. In a second step, the expert panel can review the manufacturer's intended clinical development strategy and proposals for a clinical performance study, which may particularly include proposals for PMPF. The manufacturer shall give due consideration to the expert panel's views and document this consideration in its performance evaluation report.

11.1.2 Advice for cases where the clinical performance evaluation is advanced or where the performance evaluation report is completed

Early scientific advice would be too late for manufacturers who are in an advanced stage with their clinical performance evaluation or have already drawn up their performance evaluation report.

In those cases, the expert panel's advice may be requested by a notified body in the framework of an ongoing conformity assessment procedure (see point (a) below). Manufacturers intending to submit an IVD with a potential orphan status for conformity assessment, should engage early with a notified body, discuss the orphan status and determine whether to seek advice from the expert panel.

In exceptional cases and during the IVDR transitional periods, the manufacturer itself may request such late-stage advice from the expert panel (see point (b) below).

(a) Late-stage advice requested by a notified body

Before submitting a request for advice to the expert panel, the notified body should give the manufacturer the opportunity for input into the request. Having regard to the limited capacity of the expert panels, notified bodies are advised to reach out to the EMA expert panel secretariat as early as possible to include an envisaged request in the expert panels' planning.

The advice request may concern the orphan status and possibly also the data required for the manufacturer's clinical performance evaluation, including any justification provided by the manufacturer regarding limited clinical performance data, the acceptability of clinical uncertainty, and proposed PMPF activities. For that purpose, the notified body should put forward to the expert panel specific questions for which it seeks advice. Those questions should be based on a preliminary analysis of the performance evaluation and proposed PMPF activities.

To ensure a consistent approach in the conformity assessment of orphan IVDs, the MDCG encourages notified bodies to make use of this consultation, particularly in those cases where the notified body does not agree with the manufacturer's claim that the device qualifies as an orphan IVD, or if it is uncertain in this regard, unless the expert panel has already provided advice on the orphan status directly to the manufacturer. The notified body should consult the expert panel at an early stage of the conformity assessment procedure, e.g. in the application review phase. However, the expert panel may also be consulted during the actual conformity assessment procedure if the notified body identifies any uncertainties.

Where the requested advice concerns the clinical performance evaluation, the notified body should determine the timing of the consultation in agreement with the manufacturer depending on how it fits best in the overall conformity assessment procedure.

The notified body will need to include the expert panel's considerations in its performance evaluation assessment report. If the notified body has a different view than the expert panel, it should give reasons for such divergent views in the report.

(b) Late-stage advice requested by the manufacturer

A manufacturer could still request expert panel's advice when the clinical performance evaluation is fairly advanced, or the performance evaluation report is already drafted. This situation mainly pertains to legacy IVDs that need to transition to the IVDR[19], but it could also apply to new IVDs with an already advanced clinical evaluation. Therefore, as an extraordinary measure during the IVDR transition periods, such late-stage advice may still be requested by manufacturers. The scope of this request can concern the orphan status and, if designated as an orphan IVD, also the data required for the clinical performance evaluation. The manufacturer's performance evaluation plan or its draft performance evaluation report could be suitable documents to be submitted with the request.

The advice could be requested before or after lodging an application for conformity assessment with a notified body. However, when a notified body is already involved, the manufacturer and notified body should agree that the expert panel consultation does not interfere with the notified body's assessment.

[19] See IVDR Article 110 for the different time periods and the conditions by which legacy IVDs can benefit from the transitional provisions.

To avoid any overlap with the technical documentation assessment by the notified body, a manufacturer should only request expert panel advice if the manufacturer will be able to update its performance evaluation report, taking into consideration the expert panel's views, before the notified body assesses the manufacturer's performance evaluation[20]. If a timely update of the performance evaluation report is not possible, consultation of the expert panel should be left to the notified body (see point 11.1.2(a)).

11.2 Timelines for expert panel's advice

Where the expert panel's advice to a manufacturer or to a notified body is limited to the question whether an IVD meets the criteria of an orphan IVD, the expert panel will endeavour to provide its advice within 60 days.

Where the expert panel's advice concerns both the orphan IVD status and the data used by the manufacturer for its clinical performance evaluation, the expert panel will endeavour to provide its advice within 90 days, provided it is simple advice. The advice should clearly distinguish between the expert panel's views on the orphan device status and its views on clinical performance data related aspects.

If considered appropriate by the expert panel, it can provide its advice in two steps: first advice on the orphan IVD status and second advice on the clinical performance data.

11.3 Relationship with PECP

In case of class D orphan IVDs, the PECP described in IVDR Article 48(6) could apply. In such a case, advice provided on the orphan status and/or the clinical performance evaluation and how it has been taken into consideration should be reflected in the manufacturer's performance evaluation report that is submitted for PECP. The notified body should take into account that the PECP prescribes that the performance evaluation report should be provided to the 'expert panel on IVDs' within five days of receiving it from the manufacturer.

[20] This is possible for IVDs for which the manufacturer has not yet submitted its performance evaluation report to the notified body. Indeed, for the purpose of meeting the conditions for the extended IVDR transition periods, the manufacturer's application with a notified body does not necessarily include documentation that is not needed for the conclusion of the written agreement and that is likely to be updated by the manufacturer before the actual conformity assessment.

12. Annexes

Annex 1

Examples of orphan IVDs

Note that the examples[21] below could become outdated in the future in case any of the criteria that determine the orphan IVD status are no longer fulfilled (e.g. when sufficient alternatives become available).

Example 1	
IVD: **Targeted NGS panel** intended to detect clinically relevant mutations (e.g. in *EIF6*, *TP53*, *RUNX1*, *SETBP1*), as well as somatic reversion (e.g. in *SAMD9*, *SAMD9L*, *DKC*, *TERT*) in the context of **Inherited Bone Marrow Failure Syndromes** (IBMFS).	
Incidence in EU[22]	Example of an IBMFS: Shwachman-Diamond syndrome (<100/year).
Available alternatives?	No CE-marked IVD is specifically validated for IBMFS somatic molecular profiling. Standard commercial myeloid or lymphoma panels do not include all necessary targets.
Expected clinical benefit	Prognostic information, support for therapy selection (e.g. time-point of stem cell transplant) and improved disease classification.

Example 2	
IVD: **Ektacytometry** is a laser diffraction-based functional laboratory assay that evaluates red blood cell deformability under varying osmotic conditions and shear stress. The test generates a characteristic deformability profile reflecting the biophysical properties of the erythrocyte membrane, which is influenced by membrane composition, cytoskeletal integrity, and cell hydration status for the diagnosis of **Hereditary Erythrocyte Membrane Disorders** (HEMD). It provides functional information that cannot be obtained through morphology or genetic testing alone.	
Incidence in EU	HEMD are a heterogeneous group of rare conditions, such as hereditary spherocytosis (HS), hereditary pyropoikilocytosis and hereditary stomatocytosis, characterized by altered erythrocyte hydration and haemolytic anaemia. Except for HS, which has a borderline prevalence of 1 in 2,000–5,000 individuals in Europe, the prevalence of the other disorders is considerably lower and varies depending on the specific condition, with reported estimates ranging from approximately 1 in 8,000–55,000 individuals for dehydrated hereditary stomatocytosis to around 1 in 100,000 individuals for ultrarare entities. Data on annual incidence are currently limited or unavailable for most of these conditions. However,

[21] Examples provided by Biomedical Alliance in Europe and MedTech Europe
[22] Based on 3,67 million births per year or on a population of 450 million people in the EU (data from Eurostat)

	considering that the assay is intended for use in specialized diagnostic settings and primarily for diagnostically complex or atypical cases of HEMD, the total number of individuals in the EU expected to undergo testing annually is estimated to remain well below 12,000.
Available alternatives?	No CE-marked IVD is specifically validated for the functional differential diagnosis among hereditary erythrocyte cell membrane defects. Current diagnostic approaches rely primarily on genetic testing, which often identify a large number of variants of uncertain significance (VUS) that do not allow a clear or clinically actionable diagnostic classification in these patients.
Expected clinical benefit	Supports definitive diagnosis in diagnostically challenging cases, including patients with inconclusive genetic findings or VUS in disease-causing genes. Enables improved disease classification and prognostic assessment, particularly in distinguishing stomatocytosis from phenotypically overlapping membrane disorders. Informs clinical management and therapeutic decision-making, including avoidance of inappropriate interventions and consideration of targeted or emerging therapies.

Annex 2

Performance Evaluation Report (PER)

2.1 Orphan IVD-specific information to be included in the PER

As part of the general requirements regarding the PER for all IVDs, the manufacturer should ensure that the PER includes summary descriptions of the orphan IVD-specific considerations laid out in this guidance, including:

- summary of how the IVD meets the criteria for orphan status, per section 4;
- summary of any identified limitations in clinical performance data and residual risks, including a description of how these were identified;
- acceptability of these limitations in clinical performance data and residual risks, per section 5, with particular justification that:
    - all available performance data have been evaluated[23], and any limitations in clinical performance data have been identified;
    - the existing data is sufficient to demonstrate that the relevant GSPR in IVDR Annex I are met, that the benefit-risk ratio is acceptable, and that it is expected that the IVD will provide a clinical benefit taking into account the clinical condition, the state of the art, and the safety of patients;
    - it is not feasible or proportionate to generate further clinical performance data within an acceptable timeframe in the pre-market setting;
    - the manufacturer has adequate PMPF and PMS plans that will timely generate data that will fully address the remaining limitations in clinical performance data as far as possible;
    - users of the IVD will be adequately informed of the orphan status, of the limitations in pre-market clinical performance data, and on how to report incidents, complaints, and other clinical experience to the manufacturer (by provision of information on the labelling, in the IFU, summary of safety and performance, and/or other accompanying documentation).
- summary of the applicable non-clinical data that was evaluated as part of clinical performance evaluation planning, per section 6;
- summary of pre-market clinical performance data that have been identified and evaluated, including any clinical performance studies, with due regard to sections 7 and 8;
- a clear, stringent, and detailed PMPF plan[24] with due regard to section 9, including:
    - summary of the risk management plan as described in section 9.1;

[23] Per IVDR Annex XIII

[24] This may be documented in the PER or be a separate 'PMPF Plan' document that is referenced in the PER.

  - description of the type and quality of data that needs to be generated in the post-market phase in order to further evaluate the clinical performance and clinical safety of the device and address identified limitations in clinical performance data;
  - description on how the manufacturer plans to generate these data in an appropriate, timely manner;
  - projections on the number of persons that will be tested with the IVD per year in the EU;
  - a summary of planned PMPF activities including, as applicable, PMPF studies.
- summary of any interaction with an expert panel as described in section 11;
- a plan to update the PER at pre-defined intervals as appropriate, based on the PMPF plan, and whenever new information becomes available that may change the benefit-risk profile of the orphan IVD.

2.2 Post-market updates to the PER

As part of updates to the PER in the post-market setting, the following orphan IVD-specific information should be highlighted and kept up to date as necessary, based on the latest available information:

- up-to-date information with respect to the orphan IVD status, per section 4;
- total product sales in the EU and worldwide;
- summary of state of the art, highlighting any changes to available alternatives (if any);
- updates on clinical evidence, including any changes to limitations in clinical performance data;
- summary of up-to-date determination of benefit-risk ratio;
- summary report of ongoing PMPF activities and their progress towards addressing limitations in pre-market clinical performance data.

Annex 3

Extrapolation of clinical performance data to orphan indications

3.1 Key aspects

IVDs that are intended to be used for orphan populations/indications, may have clinical performance data from their use in non-orphan populations/indications. In some circumstances, it may be appropriate to extrapolate these clinical performance data for the purpose of clinical evaluation of the intended use in the orphan population/indication.

The appropriateness of this extrapolation should be considered on a case-by-case basis, and will depend on several factors, including the characteristics of the IVD, existing information of the IVD in the non-orphan population/indication, what is known or can be extrapolated about the IVD to the intended orphan population/indication, and the underlying disease/condition/circumstance.

The extent to which extrapolated clinical performance data can be relied upon will vary from IVD to IVD. In general, it is anticipated that extrapolated clinical performance data could be combined with other clinical performance data to provide sufficient clinical evidence for the purpose of approval of the orphan indication (so-called '**partial extrapolation**'). Less commonly, it may be appropriate for the extrapolated clinical performance data to provide sufficient clinical evidence for the orphan indication without requiring additional clinical performance data (so-called '**full extrapolation**'). In both cases, the appropriateness of this extrapolation will need to be evaluated and justified by the manufacturer and assessed by the notified body. The notified body may consider the extrapolated data alongside any other existing non-clinical and clinical performance data and the PMPF plan. The PMPF plan should build on the existing data, to evaluate the safety and performance of the IVD throughout the IVD's lifecycle for its orphan intended purpose.

- **Partial extrapolation**: extrapolated clinical performance data are combined via a suitable statistical model or methodology with other sources of clinical and non-clinical data, to provide sufficient clinical evidence to support the orphan indication/intended purpose. The construction of such a statistical model is anticipated to require the availability of measured variables that will help connect the available outcomes to the outcomes of the intended orphan population/indication. If the necessary variables are not available in the data sources, partial extrapolation may not be appropriate. If the model is determined to be appropriate, then the inferences obtained from it may be used to support the orphan device indication.
- **Full extrapolation**: extrapolated clinical performance data are used as the main or sole source of clinical performance data (i.e. a complete substitute) to provide sufficient clinical evidence to support the orphan indication/intended purpose. Minimal to no additional clinical performance data are needed for the purpose of initial certification of an orphan indication/intended purpose.

The appropriateness of extrapolation of clinical performance data from use in other (sub)populations/indications depends on three main factors:

- the relevance of the data, including the similarity of characteristics between the proposed orphan (sub)populations/indications, and the others from which the data were collected;

- the quality of the data and their suitability; and
- the extent to which the data can provide sufficient clinical evidence to assess the safety, performance and expected clinical benefit for the orphan indication.

3.2 Decision process for considering extrapolation

To determine the suitability of clinical performance data for extrapolation, the following steps from Figure 1 should be followed and documented in the performance evaluation report.

I. Suitability for extrapolation of clinical performance data

Are the clinical performance data relevant to the orphan (sub)population(s)/indication? Clinical performance data can be considered relevant for the purposes of data extrapolation if it is justified that:

(a) the indication(s) for the IVD is the same, but in a different population;
(b) the endpoint(s) or outcome(s) that has been measured in the non-orphan population is the same or similar as would be measured as an endpoint when used in the intended orphan population; **and/or**
(c) the clinical performance data from the non-orphan population provide validated surrogate endpoints that are expected to be relevant to the orphan population.
   - In this case, a reliable and valid model might be used to predict the endpoint for the orphan population using clinical performance data from the other population, e.g., a validated surrogate endpoint in the available data set(s) that has been shown to predict a different, longer-term endpoint of interest.

- If **ANY** of I(a)-I(c) is **TRUE** → potentially suitable for extrapolation; **proceed to II**.
- If **NOT** → unsuitable; do **NOT** extrapolate.

II. Determining the extent of extrapolation

Do the characteristics of the IVD, patients, or diseases/conditions/circumstances differ between the orphan and other (sub)populations/indications to an extent that the expected safety and/or performance of the IVD could be impacted in a clinically meaningful way? In particular, are there clinically meaningful differences with respect to:

(a) sample collection, matrix, pre-analytical steps?
(b) characteristics of the IVD?
(c) patient characteristics?
   - E.g., characteristics that are unique to the orphan (sub)population/indication that may impact the IVD's expected safety/performance. For example, special considerations may be needed with respect to physiological differences related to age, sex or ethnicity.
(d) disease characteristics between the two populations/indications?
(e) any other relevant differences or factors?

Other factors that may limit extrapolation include:

- insufficient knowledge of the disease/condition/circumstance in the intended (sub)population;
- no suitable statistical methodology has been identified for the purposes of partial extrapolation and combination with other clinical performance data, e.g., the expected differences between the two (sub)populations/indications;
- the clinical performance data from the non-orphan population were obtained from use of the IVD outside its intended purpose;
- the state of the art has changed since the creation of the data to such an extent that historical data would likely be different to new prospectively collected data.

- If **ALL** of II(a)-II(e) are answered "**NO**" → potentially suitable for FULL EXTRAPOLATION; appraise and analyse the clinical performance data and **proceed to III**.
- If **ANY** of II(a)-II(e) answered "**YES**" → potentially suitable for PARTIAL EXTRAPOLATION; appraise and analyse the clinical performance data and **proceed to IV**.

III. Suitability for full extrapolation

Are the extrapolated clinical performance data of sufficient amount and quality to provide sufficient clinical evidence for the evaluation of the IVD's safety, performance, and clinical benefit for the orphan indication?

- If "**YES**" → likely suitable for **FULL EXTRAPOLATION**; conduct clinical evaluation accordingly.
- If "**NO**" → potentially suitable for **PARTIAL EXTRAPOLATION**; **proceed to IV**.

IV. Suitability for partial extrapolation

Despite any differences or limitations identified, are the extrapolated clinical performance data suitable for use as part of the clinical evidence for the orphan indication?

- If "**YES**" → likely suitable for **PARTIAL EXTRAPOLATION**; conduct clinical evaluation accordingly.
- If "**NO**" → do **NOT** extrapolate.

Fig. 1 - Decision process for considering extrapolation of data to orphan IVD (sub)population(s) (Part A)

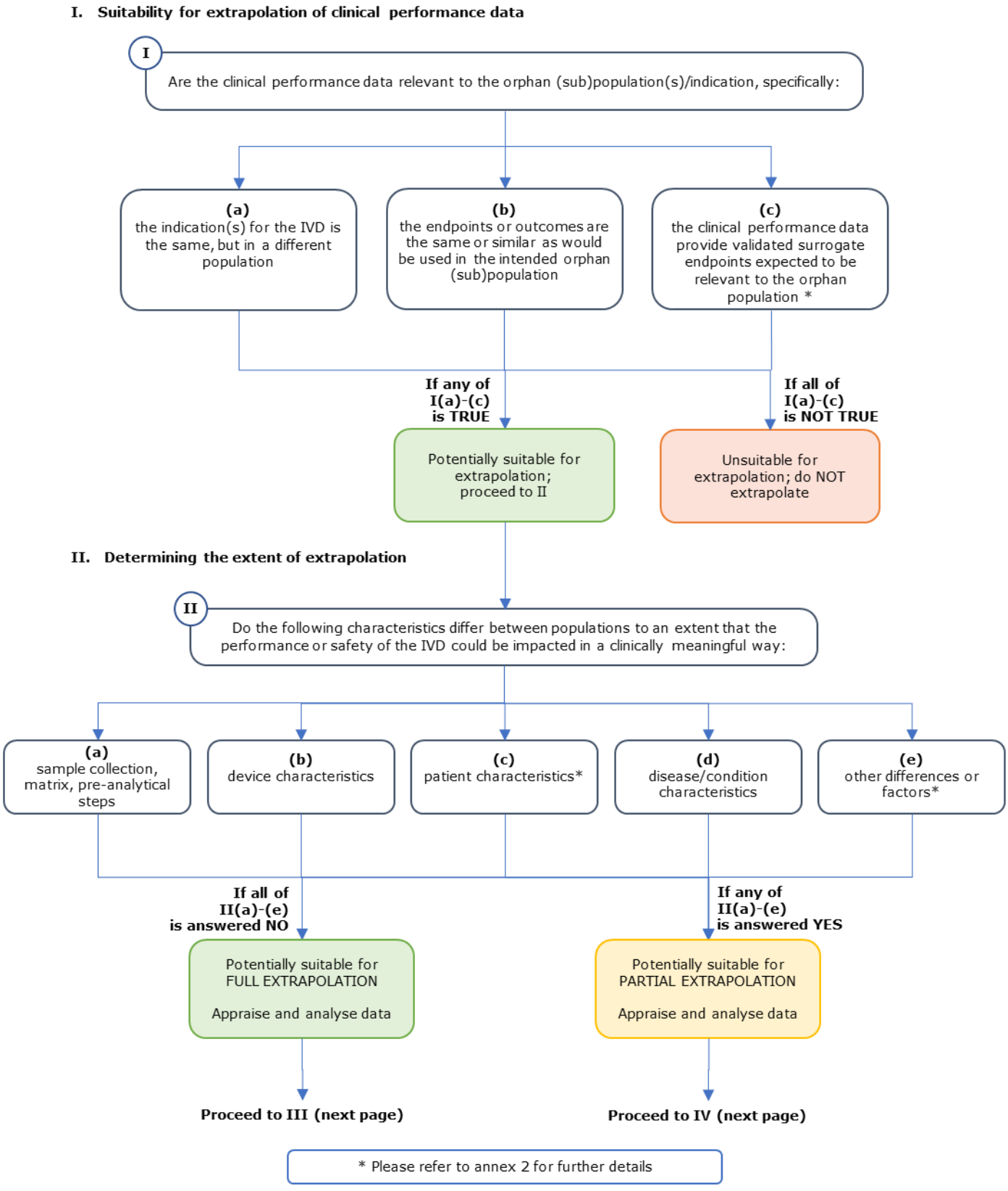
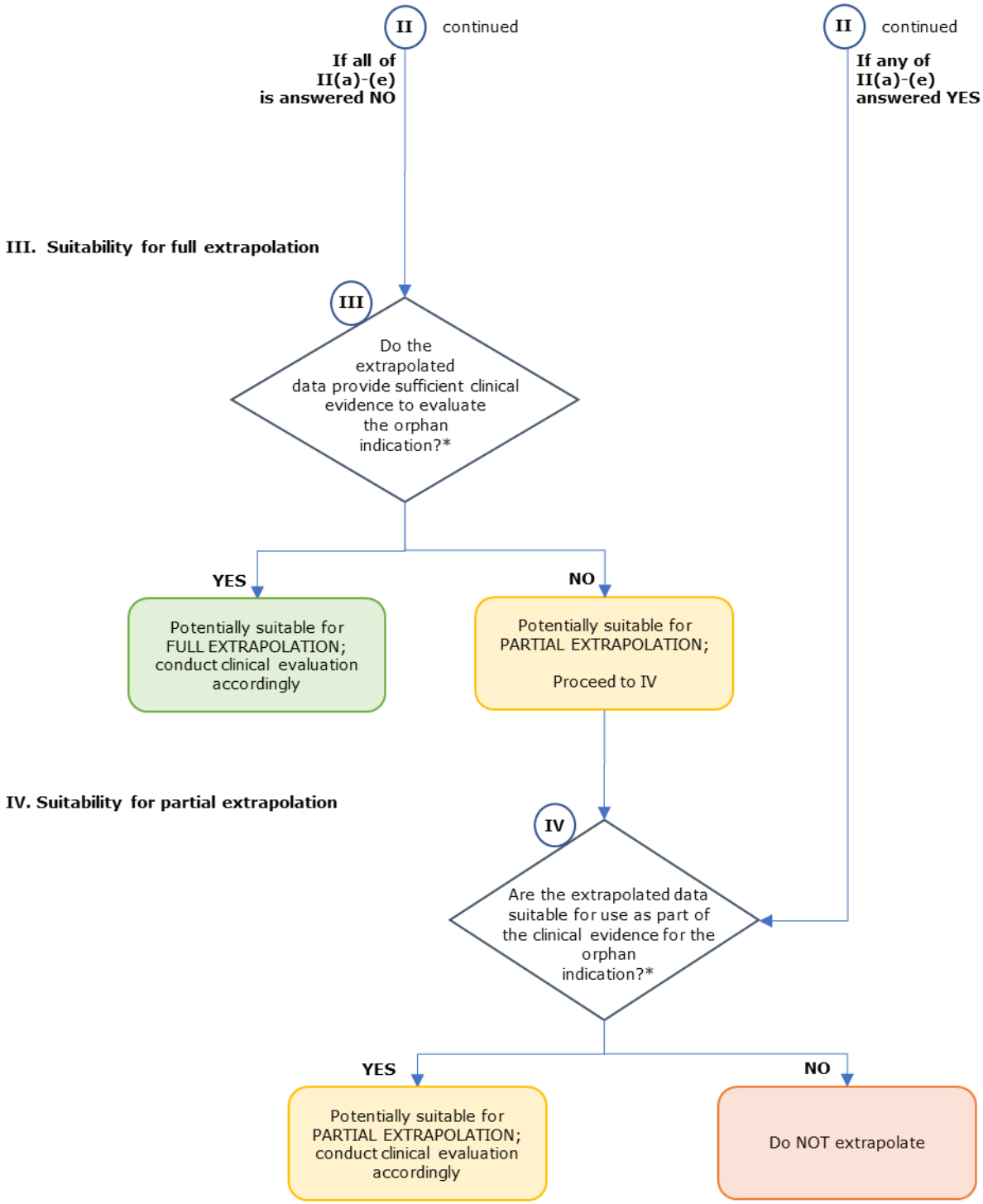


Fig. 1 - Decision process for considering extrapolation of data to orphan IVD (sub)population(s) (Part B)



Annex 4

Considerations for clinical performance studies with orphan IVDs

4.1 Introduction

The purpose of this section is to provide considerations for IVD manufacturers when designing a clinical performance study for an orphan IVD. It is not intended to be an exhaustive or prescriptive list of requirements with respect to study characteristics. As with all performance studies, it is expected that performance studies of orphan IVDs will be designed and conducted in compliance with IVDR requirements and in line with relevant good clinical practice principles. For more guidance on IVD performance studies, please refer to MDCG 2022-2 (General principles of clinical evidence for IVDs), MDCG 2025-5 (Q&A regarding performance studies of IVDs), EN ISO 20916 (Clinical performance studies using specimens from human subjects) and MDCG 2024-4 (Safety reporting in performance studies of IVDs).

4.2 Defining the study population

As for all IVDs, careful definition of the study population is key and the acquired study specimens should adequately reflect the intended target population. As the disease/condition/circumstance that the orphan IVD tests for, or the circumstances it is used in, should not present in more than 12.000 individuals per year, the target and study populations can be quite narrow. In this respect, the intended function of the IVD plays an important role: in general, the target population for a screening IVD is wider than for a diagnostic IVD, while a confirmatory IVD can be linked to an even smaller target population. As mentioned previously, significant performance challenges may be encountered if an orphan IVD is applied to the general population, in particular in the context of wide screening applications. Owing to the low prevalence of the condition within the population, appreciable levels of false positive results may be expected based on statistical factors. Defining and focusing the population to be tested can reduce the expected false positive rates and improve positive predictive values.

To this point, inclusion and exclusion criteria for the clinical performance study should be such that a sufficient number of target population specimens can be tested in order to decrease sampling variability and increase statistical precision. In many instances, positive clinical specimens for orphan IVDs are scarce and/or difficult to collect in sufficient quantities. Consequently, careful consideration should be given to possible sample selection bias, e.g.: are all specimens derived from a single clinical site versus multiple sites, are sites from which specimens are acquired representative for the sites for which the IVD is intended to be used, are specimens representative of the full possible range of the assessed analyte, are all population subgroups covered, etc. The clinical performance study plan should include the measures taken to minimise sample selection bias. In addition, when choosing an appropriate study population sample size, manufacturers should already plan if and how many extra specimens might be needed during PMPF studies (see section 9).

4.3 Objectives

For IVDs, performance and safety are intrinsically linked as underperforming IVDs will indirectly harm patients, e.g. by providing no, delayed or false results and/or by inducing wrong patient management.

Therefore, the focus of clinical studies with IVDs lies primarily with performance. While primary objectives of clinical performance studies with orphan IVDs thus concentrate on performance and benefit-risk ratio, further PMPF studies should aim to evaluate the overall safety, performance, and clinical benefit of the orphan IVD throughout its life cycle, with a suitable focus on long-term endpoints.

4.4 Selection of endpoints and study design

Clinical performance endpoint(s) should be predefined on the basis of relevant indicators to assess the clinical performance outcome and clinical benefit. The appropriateness and relevance of the chosen endpoints should be clearly justified in the clinical performance study plan, to help regulatory authorities, notified bodies, and the expert panels (as applicable) understand and accept these endpoints. Continuous monitoring of safety through regular reporting of serious adverse events and of relevant device deficiencies is key throughout the orphan IVD evaluation program.

The choice of study design should be carefully considered in terms of its strengths and limitations (e.g. vulnerability to bias or confounders). E.g. prospective specimen collection during the study is under the control of the investigator, helping to ascertain that the study population is a proper representation of the target population. However, a timely prospective study design is often not possible when the target condition is rare. In these circumstances, retrospective specimen collection using specimens from biobanks is more convenient, provided that the potential bias (e.g. regarding specimen characteristics, specimen information and storage conditions) associated with retrospective specimen selection is adequately perceived and controlled. The choice of study design needs to be justified and appropriately documented (e.g., in the clinical performance study plan and/or PMPF plan). Consideration needs to be given with respect to minimisation of bias, representativeness of the study, and transparency of the study findings.

For studies of orphan IVDs, where generating large amounts of prospective evidence is challenging in the premarket setting, simulations anchored in high-quality real-world evidence and calibrated by relevant data derived from clinical performance studies can help stress-test assumptions, quantify uncertainty, and inform potential performance when applied to larger cohorts. While these simulations should not be used as a substitute for direct empirical testing, they can provide valuable support in contextualizing study results in orphan populations. The design and use of simulated data should be pre-specified and thoroughly documented. Results from appropriate simulations can assist in informing interim decision-making; however, confirmation of actual device performance should be established through larger, long-term studies and post-market activities.

4.4.1 Adaptive and sequential designs

Adaptive and sequential designs are based on interim analyses planned to be carried out in the course of the clinical performance study.

Adaptive studies may allow for potential changes in several parameters (e.g. sample size requirements, number of analyses) as the study progresses. However, care should be taken to ensure the integrity of the study is not compromised as a consequence of excessive or unnecessary adaptations. Where possible, all anticipated or potential adaptations of the study should be described in the performance study plan, based on anticipated results of the planned interim analyses.

Sequential designs are mainly based on interim analyses of the study's primary endpoints, and unlike adaptive clinical performance studies, no adaptation of parameters is allowed. Instead, the stepwise methodology allows for continued, periodic analyses after each predefined group/cohort/stratum of patients reach their outcome, thus allowing for interim opportunities to determine whether there is sufficient evidence of clinical benefit or lack thereof.

Although adaptive and sequential methodologies can provide more flexibility, it is important to note that this approach can be vulnerable to type I (false positive) error. This potential for error should be considered when evaluating clinical performance data generated from these study designs.

Where appropriate, interim analyses may be enough to support the initial clinical evaluation for conformity assessment. In this event, where possible and where there still is equipoise, the study should continue to completion as planned in the study plan, to ensure continued collection of clinical performance data and to ensure appropriate long-term follow-up for the study participants.

4.5 Statistical considerations and Bayesian approaches

For many performance studies of orphan IVDs, frequentist approaches to statistical analysis can be particularly challenging, as patient recruitment from an orphan (sub)population may make inferential statistical analysis unachievable or inappropriate. In such cases, descriptive statistical methods, or in some situations, alternative methods to frequentist approaches such as Bayesian approaches, may be more appropriate.

Bayesian approaches cover a very broad range of possibilities. In Bayesian analyses and hybrid Bayesian analyses, probability statements are made on the basis of accumulated data combined with prior (existing) data. In this sense, Bayesian approaches can also be considered adaptive.

Use of an external control, including historical control data from sources such as prior studies or ongoing registries, might be a viable approach too if it helps to improve the interpretability of the performance study data. Care should be taken so that only patients with the same disease/condition/circumstance and comparable clinical and demographic characteristics are used as controls.

While the use of prior data is not unique to Bayesian applications, the expression of belief about prior data is however different in this framework. Belief about prior data (e.g. from literature, experts, registries) is expressed in the form of a plausible distribution. Observed data from the study are then collected and when combined with the belief about the prior data/evidence, an updated prior, known as the posterior belief (distribution) is determined. In this way, accumulated observed data combined with historical knowledge and expert opinion forms a basis for continued evaluation.

A potential advantage of using Bayesian approaches is avoidance of the constraints of the type I error which are associated with larger sample sizes. However, the absence of a type I error, does not mean that Bayesian approaches are free from other decision errors, and these should be considered. The flexibility to form a prior which expresses more or less uncertainty about prior belief can impact the sample size requirements.

Alternatively, a 'hybrid Bayesian' approach can be considered, which allows expression of uncertainty in the historical data, while allowing use of the frequentist approach. The justification for expression of

prior belief around existing data should be rigorously supported with clinical and statistical evidence as this can have a meaningful impact on the conclusions of the study results.

Other approaches may also exist which are less commonly used, for example, decision theoretic, value of information, and meta-analytic (including Bayesian evidence synthesis) approaches could be used. However, extreme care should be exercised to ensure the methodologies are pre-specified and the clinical interpretation is clear, to avoid data driven approaches which may increase the chance of a false conclusion.

4.6 Choice of comparator

In general, the clinical performance of an IVD should be assessed against a reference standard (also known as a 'gold standard'), i.e. the best possible diagnostic method for the target disease/condition/circumstance. When a reference standard is unavailable or is impractical to use, an IVD for performance study may be compared to an already available CE-marked IVD and a positive and negative percentage agreement will be obtained. However, given the large number of rare diseases/conditions/circumstances, there will often be situations where neither a reference standard, nor a CE-marked IVD exists for comparison. Whatever the particular study situation, the manufacturer should specify in its clinical performance study plan what comparator will be used or should justify why a comparator is not applied and how the 'true clinical status' of study subjects will be determined.