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Questions and answers on the information session on the pilot for expert panels' advice for orphan medical devices

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1. Introduction

This Q&A document was prepared following the webinar held on 23 September 2024 to inform stakeholders on the EMA pilot for expert panels' advice for orphan medical devices. It provides answers to the most frequently asked questions received before, during and after the webinar. Reference is made to the presentations for further information.

What is this new pilot on orphan medical devices about?

Clinical evidence requirements from Regulation (EU) 2017/745 on medical devices (MDR) present a challenge for devices specifically intended for use in rare diseases/conditions ('orphan populations'), or in rare cohorts of patients with an otherwise non-rare disease/condition ('orphan subpopulations'). Proactively generating clinical data within an appropriate timeframe in small patient populations is particularly challenging, as is the case for vulnerable populations such as infants and children.

The Medical Device Coordination Group (MDCG) developed specific guidance (MDCG 2024-10) that contains the criteria for devices to qualify for orphan device status, as well as the resulting clinical evaluation and procedural considerations for orphan devices.

Under this pilot, manufacturers and notified bodies may seek advice from the expert panels on the orphan device status and on its clinical development or evaluation.

2. Questions and answers

Part I – General considerations

2.1. Can the orphan device guidance be applied to devices already placed on the market under the MDR?

At present, confirmation of the orphan device status after the device is placed on the EU market is outside of the MDCG guidance document and outside the scope of the scientific advice pilot launched by EMA. However, there are cases where confirmation of the orphan device status could be applicable, for instance, for extension of an intended purpose of a medical device, if the extension covers an orphan subpopulation, and for the clinical evidence package required for a change in the device, if there are significant changes to a device that may potentially impact the benefit/risk balance in a small population of patients. These cases will be analysed on a case-by-case basis.

2.2. How will the information that a device received orphan device status be conveyed to the users?

According to MDCG 2024-10, the "users of the device will be adequately informed (e.g. by provision of information in the instructions for use, on the summary of safety and clinical performance (for implantable and class III devices), and/or other accompanying documentation) of the orphan status of the device, the limitations in pre-market clinical data, and instructions to users on how to report incidents, complaints, and other clinical experience to the manufacturer".

2.3. Are there any specific labelling expectations?

Labelling requirements for medical devices, including orphan devices, are in the remit of notified bodies. Therefore, notified bodies will communicate to manufacturers any labelling requirements as applicable.

2.4. How specific is the definition of orphan with regards to 12,000 patients?

In MDCG 2024-10, a medical device is to be considered orphan if it "is 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 at least one of the following criteria are met:
- 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".

In MDCG 2024-10 section 4, guidance is provided on how manufacturers can justify that the device meets orphan device status including the epidemiological criteria. Manufacturers may also seek advice from the expert panels on the orphan device status.

2.5. Can data gathered outside the European Union be used to support the evaluation of an orphan device's safety and performance?

The clinical evidence presented must comply with the general principles established in the MDR for clinical evaluation and investigations. Clinical data gathered outside the EU may be used provided that they are relevant to the device/its intended purpose and suitable for establishing the device's safety and performance.

2.6. Is there a guideline on the required level of clinical evidence? In other words, how low must the risk of serious adverse effects be after a clinical study for an orphan device for a non-lethal but severe condition for this device to be accepted to the market?

Please refer to PART A – Clinical Evaluation Considerations of MDCG 2024-10.

The choice of the study design including the study population should be carefully considered in terms of its strengths (statistical power) and limitations (e.g. susceptibility to bias or confounders) and its ability to address any ethical and practical challenges and should be justified on a case-by-case basis; it is thus a matter of assessment.

Ultimately, the study should be designed so that the clinical data will be sufficient to demonstrate conformity with the General Safety and Performance Requirements (GSPRs) and to draw a conclusion on the benefit/risk of using the device in the orphan (sub)population. It is acknowledged that there might be limited clinical evidence available for orphan devices, particularly on performance. As for other devices, manufacturers are required to define, specify and justify both the level of evidence and the level of acceptable risk that are appropriate to the orphan device in order to draw a conclusion on the risk-benefit balance.

The consultation of expert panels will allow for additional advice on the acceptance of the risk level estimated at the time of certification, based on the proposed clinical development strategy (at the time of early advice) or the available clinical data package (at the time of late advice).

2.7. Is the common sequential approach of early feasibility study/ies that allow for risk-based assessments to inform on safety and usability/device design, followed by one or more pivotal study/ies to further inform on safety and performance of the device, also allowed for orphan devices?

Yes, such a sequential approach is allowed for orphan devices. Other approaches are also possible.

2.8. Is the Orphan Device guideline applicable to a device used in combination with a medicine that is already pursuing an Orphan Drug Designation application?

MDCG 2024-10 applies to medical devices, including medical devices co-packaged or cross-labelled with a medicinal product or medical devices with ancillary medicinal substances. It does not apply to integral medicine-device combination products (https://www.ema.europa.eu/en/human-regulatory-overview/medical-devices#medicinal-products-used-in-combination-with-a-medical-device-13037) that fall under the pharmaceutical legislation.

2.9. Can real-world evidence be used to support the clinical evaluation of an orphan device?

Yes. MDCG 2024-10 mentions several possibilities on how real-world evidence can be used in that regard.

2.10. Is there a plan to develop a guidance on risk determination and dealing with uncertainty?

ISO 14971:2019 Medical devices — Application of risk management to medical devices is a standard applicable to all medical devices and provides information on how to perform risk analysis and assessment.

In the particular case of orphan devices, MDCG 2024-10 section 9 outlines the importance of post market surveillance and Post-Market Clinical Follow-up (PMCF). It is mentioned that manufacturers should identify pre-market limitations in clinical data and uncertainty around important risks and map them into an appropriately designed PMCF plan. This plan should outline how risks will be proactively monitored, assessed, and mitigated throughout the post-market lifecycle of the device. PMCF activities could include PMCF investigations with larger datasets, suitable registries, and other sources of real-world data. The data generated from PMCF is important to enable the continued assessment of the benefit-risk profile of orphan devices with a higher degree of certainty.

2.11. Are orphan medical devices in scope of the Health Technology Assessment Regulation (HTAR)?

According to Article 7(1)(c) of Regulation (EU) 2021/2282 on health technology assessment (HTAR), class III implantable devices or class IIb active devices destined to administer or remove a medical product for which the relevant expert panels have provided a scientific opinion in the framework of the clinical evaluation consultation procedure (CECP) might be selected for joint clinical assessment. This would be applicable to orphan devices, if pertaining to any of those groups.

2.12. Can conditions applied by the notified body during the initial conformity assessment process be lifted during the re-certification process?

Yes. If the notified body comes to the conclusion that specific conditions or provisions are not any more needed for the renewal of the certificate, those conditions or provisions can be lifted by the notified body.

Part II – Procedural considerations

2.13. How and until when can developers apply for expert panel's advice? Are there limitations on the number of applications? If so, how will the applications be selected?

The pilot programme was opened on 2 August 2024 and applications are accepted since that date. The letter of interest can be accessed here: Letter of interest – Expert Panels - Employee Center (europa.eu). An EMA account is necessary to access the webform.

Applications received up to 31 October 2024 have been reviewed in November 2024 and selected as test cases for the pilot. The pilot programme will run until the end of 2025, subject to available resources, and is designed to establish a long-term process for requesting orphan device support from the expert panels.

2.14. When does the orphan device procedure starts?

The procedure starts when the final briefing document is submitted to the experts. This is preceded by an optional pre-submission step where a meeting with the expert panels secretariat is organised to discuss the requirements for the submission.

2.15. Is the dossier with questions and answers to be submitted at the time of the request for advice?

The full briefing document is requested only once the applicant receives confirmation of the acceptance of their device into the pilot.

In the first step, the manufacturer/ notified body will have to submit a 'letter of interest' by completing the dedicated form on the portal: Letter of interest – Expert Panels - Employee Center.

If selected, the manufacturer/ notified body will be asked to submit a briefing book containing on one hand the justification why the device meets the orphan criteria, and on the other hand the clinical development strategy, with any supporting development information, and the precise questions on which they would like to have input from the expert panels with their position. Templates are available to guide in the drafting of these two parts of the briefing book under EMA's orphan device pilot programme webpage:

Request for advice on the orphan device status

Request for advice on the clinical development strategy or clinical data required for the clinical evaluation

Note: These application templates in PDF format are provided for information purposes. Word documents to be filled in will be sent to the applicant during the procedure.

The EMA secretariat will organise a meeting to discuss the procedural steps leading to an advice from the expert panels on the orphan device status and/or on the clinical development questions. The procedure will typically take 60 days (orphan device status designation only) or 90 days (orphan device status designation followed by scientific advice) once the final briefing document is formally submitted.

2.16. Will the expert panel advice be published?

The expert panel's advice will not be published during the pilot programme. The format of a potential future publication of aggregated data/learnings will be discussed and communicated once the pilot has ended and the full programme is implemented.

2.17. Which clinical development data should a manufacturer have available/include in a briefing book for an early advice procedure for an orphan medical device?

The templates published under EMA's orphan device pilot programme webpage provide guidance on what data to include in the briefing book:

Request for advice on the orphan device status

Request for advice on the clinical development strategy or clinical data required for the clinical evaluation

Note: These application templates in PDF format are provided for information purposes. Word documents to be filled in will be sent to the applicant during the procedure.

2.18. Will the 'late advice' of the expert panel to the notified body be binding for the certification of the orphan device?

The advice of the expert panels is not legally binding. However, it is expected that if an expert panel provides an advice, the notified body will give due consideration to the advice. The notified body will need to consider the advice given by the expert panel in its Clinical Evaluation Assessment Report (CEAR). If the advice is not followed, the notified body should provide a justification in the CEAR on the reasons why the advice was not followed.