Q & A Orphan Medicines Development – ask the European Regulator

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Link to event: Orphan medicines development - ask the European regulator | European Medicines Agency (europa.eu)

Disclaimer

This document contains a direct record of all questions asked during the open registration period and through Slido.com or verbally the day of the event and their written answers.

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1. Orphan designation development and assessment

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In the field of rare neurodevelopmental disorders we see much interest from patient families and clinicians on treatment modalities that fall outside the usual ones. Specifically: on plant-derived products and bacterial products. We don't think there is enough regulatory guidance from EMA for developers to anticipate the standards needed to develop these botanical and microbial therapies as medicines. As a result, these products are relegated to be consumed by patients as supplements, not as approved medicinal products. Is the EMA planning to issue any guidance on the development of botanical and/or microbial medicines?	Within the European Medicines Agency (EMA), the Committee on Herbal Medicinal Products (HMPC) is responsible for compiling and assessing scientific data on herbal substances, preparations and combinations to support harmonisation in the European Union (EU) market. In particular, to support EU Member States, the HMPC establishes EU herbal monographs covering the therapeutic uses and safe conditions of use for herbal substances and preparations shown to have a well-established and/or a traditional use. However, the assessment of applications for the licensing of herbal medicinal products is usually done at a national level by the national competent authorities (NCAs) responsible for medicinal products in the EU Member States, taking into account the above-mentioned scientific conclusions (EU herbal monographs) of the EMA/HMPC. Moreover, pharmaceutical companies seeking market access for traditional herbal medicines in EU Member States need to follow national procedures. Applicants can request scientific support and advice from the HMPC at the EMA. NCAs of Member States can also consult the HMPC on scientific and regulatory aspects of applications.
Can one request an orphan designation for a combination product?	Yes, it is possible to submit an orphan designation for a fixed dose combination, in that case one application is done. In case of products that will be used in combination but not a fixed dose combination, applications should be sent in separately for the products.
Can one register an orphan drug designation (ODD) for the same indication and comparable molecule, only the one who first get a marketing authorisation (MA) will benefit from the orphan exclusivity? If there is a valid ODD in place, but there is no MA application yet, can another company submit own ODD application for the same indication a substance?	Several sponsors can hold an orphan designation for the same/similar active substance/products and condition. The first product to reach marketing authorisation could get the market exclusivity (provided the orphan criteria are still met) and subsequent products will have to be compared for orphan similarity.
Considering that the ODD also exists in the US, is there any strategic advantage of following a	Orphan designation can be given at an early stage based on non-clinical data in both jurisdictions and therefore it is possible to do applications in parallel.

Question	Answer
specific order to request this designation from the agencies (FDA or EMA first)?	An option can be to do it first in the region where the sponsor is based or planning to do the initial development.
Considering that the ODD can be requested at any time during drug development as long as a significant benefit is demonstrated, would proof-of-concept research-grade nonclinical data in a relevant *in vivo* disease model be considered sufficient to demonstrate significant benefit?	Non-clinical data can be used in support of the criterion of significant benefit. The importance is to have a comparative element to the data. The best supportive data in this case is to have the approved product(s) in the study in order to be able to show any differences.
What is the Agency's view on obtaining orphan designation for a subset of a patient population of higher prevalence than 5 in 10.000, e.g. where the subset of patients do not benefit from available treatment options?	From Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03): In applications where the proposed orphan indication refers to a subset of a particular condition, a justification for restricting the use of the product would be needed. Patients in the subset should present distinct and unique evaluable characteristics with a plausible link to the condition and such characteristics should be essential for the product to carry out its action. In particular, the genetic subtype/profile and pathophysiological characteristics associated with the subset should be so closely linked to the diagnostic and/or preventive and/or treatment action of the product that the absence of these characteristics will render the product ineffective in the rest of the population suffering from the condition.
What is the position of Orphan Medicines/EMA of using so called in vitro diagnostic companion diagnostics to pro-actively select the patients likely to respond to the new therapy? Required/recommended/optional/discouraged/ incentivised?	By definition, companion diagnostics are meant to select patients eligible or, on the contrary, non-eligible for treatment with certain medicines. The indication(s) or contra-indication(s) of these medicines restrict the target population based on biomarkers which are ascertained with the use of the companion diagnostics. Ascertainment of the biomarker is therefore a prerequisite for the correct use of the medicinal product and hence the development and use of the respective companion diagnostic(s) can only be supported.
Are the incentives to developing orphan medicines considered to be adequate? What are the criteria for adequacy of incentives?	To our knowledge there are no criteria for adequacy of the incentives, however, there has been research done about the impact of the orphan regulation in preparation for the revision of the regulation: Orphan Regulation study_final report_anonymised (europa.eu)

Question	Answer
As there are so many rare and ultra-rare diseases, the reality is health technology assessments (HTAs) do not have bottomless pockets. Is there a list of priority rare diseases that could be shared with developers?	EMA has not issued a list of priorities, however, it is fair to say that development is any disease area where there are no treatments available is encouraged.
Is the criteria related to significant benefit respect to existing methods specific of EMA? Is not the same for FDA?	The criteria of significant benefit, which has to be shown in case there are satisfactory methods approved for the condition, is specific to the European orphan legislation. The US legislation does not have the same requirement.
How to demonstrate significant benefit at orphan maintenance in an indication in which new medicinal products have been approved during the clinical development of the intended orphan medicinal product?	This is a recognised challenge, and it is best to plan accordingly and prepare for indirect comparisons.
We develop personalized cancer vaccine which is patient specific and tumour agnostic. It would be safe and potentially effective for patients with very rare cancer. How do we get conditional market authorization?	Applicants may be granted a conditional marketing authorisation for such medicines on less comprehensive clinical data than normally required, where the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required. Please see more: Conditional marketing authorisation
is it possible to engage with the agency prior to the orphan application submission to receive help preparing the submission? Are informal interactions by email possible before ODD submission?	Yes, that is possible. The best option is to ask for a pre-submission meeting. A request for the pre-submission meeting is done via the IRIS portal.
Are ODD parallel evaluations by EMA and FDA possible in a structured procedure?	No, there is no official parallel orphan designation procedure between EMA and FDA.
How come only the few rare diseases with the biggest percentage of the population are of interest in research, hence proper medication available? Cause of 'big pharma gain'? Meaning even a bigger percentage of the patients left in cold! There is still a strong unmet need in the rare disease space, as evidenced by some of the data points shared. What do you think are the strongest challenges towards orphan medicines development, and are these being appropriately addressed?	For some of the rare diseases with higher prevalence (but still under the threshold of 5 in 10.000) drug development has led to medicinal products on the market, mostly because of scientific knowledge of the disease pathology and actionable targets. However, it has to be noted, that some ultra rare diseases have been focus of attention and successful development as well. It is clear that medicinal product development in very rare patient populations is challenging both due to the fact that there might be limited knowledge of the disease and the few patients available to include in clinical studies.

Question	Answer
What kind of data is required to ask for ODD in case no specific animal model exist for a certain disease? Is in-vitro data accepted? In case no specific animal model exist for a certain disease, are in vitro data accepted for the ODD?	If the sponsor is able to demonstrate that disease specific non-clinical models of the condition applied for do not exist, then medical plausibility may be argued based on in vitro data only or in combination with some extrapolations. It is known however, that the predictive value of in vitro data is lower than that of non-clinical data, therefore such cases belong to the exceptions.
Did I understand correctly that a list of drug with orphan designation is available via IRIS portal? If non, where can I find the list?	Public - List of Opinions on Orphan Medicinal Product Designation · IRIS (europa.eu)
Does the COMP SA follows exactly the same way as for the CHMP? Also on IRIS?	Yes, applications for both scientific advice and protocol assistance are done via the IRIS portal.
Ate there recommendations on selection of outcome measures for trials in rare diseases? And for single case experimental designs in particular? What are views on use of Proms as primary outcome measures?	There are specific guidelines for the development of medicinal product of some rare diseases. The outcome measures and other clinical development considerations are mentioned in those documents. For the majority of rare diseases, the most appropriate outcome measures, including patient reported outcome measurements (PROM) and other aspects of the development programme can be discussed between sponsor and EMA through protocol assistance.
Were there cases where granted ODD needed to be withdrawn because national authorities did not agree that the product is a medicinal product but a cell product falling outside of medicinal product regulations?	We are currently not aware of any such case. However, it could theoretically happen, as the legal status of a product receiving orphan designation is not decided upon at the designation stage.
Advance therapy medicinal products (ATMPs) in rare diseases have the potential to have life changing benefits to patients, does the Committee for Orphan Medicinal Products see the potential for additional supports to ATMPs that are being developed for rare genetic diseases?	Apart from the support measures that are applicable for all medicinal products, academic and non-profit organisations involved in developing promising ATMPs can apply for EMA's increased support in meeting regulatory requirements. Please see more: Advance therapy medicinal products
Half a year is quite a long time for people with a limited lifespan that have no treatment options. How to increase also your (EMAs) sense of urgency around rare disease development and learn from the covid experience how to accelerate it?	There are several possibilities to speed up regulatory procedures including orphan designation, protocol assistance and also marketing authorisation via the accelerated assessment. However, it is critical that a thorough assessment is done in order to get safe and efficacious medicines to the patients.

Question	Answer
	In addition, the ultimate access to treatment is outside the remit of EMA and relies on reimbursement on a national level.
1.1 Orphan marketing authorisation	
If there is an MA application submitted based on ODD can the MA application be based on well-established use route?	Yes, an orphan marketing authorisation application can be sought under any legal article.
Can the period of data exclusivity be shortened and be less than 10 years?	Theoretically this is possible, according to Art 8.2 of REGULATION (EC) No 141/2000: 'This period may however be reduced to six years if, at the end of the fifth year, it is established, in respect of the medicinal product concerned, that the criteria laid down in Article 3 are no longer met, inter alia, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity. To that end, a Member State shall inform the Agency that the criterion on the basis of which market exclusivity was granted may not be met and the Agency shall then initiate the procedure laid down in Article 5. The sponsor shall provide the Agency with the information necessary for that purpose.' However, in reality this has never happened.
Does the EMA consider other criteria in approval of an ODD application, apart from 'significant benefit', when there is already a competitor orphan product on the market?	All the criteria laid down in regulation No 141/2000 are checked. The prevalence has to be below 5 in 10.000, the intention to treat the condition has to be supported with data (called the medical plausibility) and finally the significant benefit has to be supported.
If there is already a marketed orphan medicinal product on the market (in current exclusivity period), is there any case for EMA to approve another product for same indication and have both products on market at same time?	Definitely, however, the new product must first be found to not be 'similar' to the approved orphan product. If the new product is not similar, the orphan criteria are reviewed and if confirmed the new product can come to the market as an orphan product. In case the criteria are not confirmed, the new product can still enter the market but as a non-orphan product.
How exactly can a company obtain extra 2-year paediatric exclusivity for a marketed orphan product. Is it full completion of clinical trial committed to in paediatric investigation plan	The market exclusivity period is extended by two additional years for an orphan-designated condition when the results of specific studies are reflected in the summary of product characteristics (SmPC)

Question	Answer
(PIP)? When exactly does 2-year paediatric exclusivity begin, at end of 10-year orphan exclusivity?	addressing the paediatric population and completed in accordance with a fully compliant PIP. The two years begin at the end of the 10-year exclusivity.
The EC's definition of non-similarity (REG No 847/2000, par. 3.2) for gene therapies seems to reward competitor products even if they are clinically inferior, as It just takes into account 'differences', they do not need to imply superiority.	The first test of any new product is the orphan similarity assessment. If an orphan designated product is deemed to not be similar, the criteria of orphan designation will be reassessed. For the new product to come to the market as an orphan it has to show significant benefit over the approved product.
1.2 Orphan incentives	
Has there been a survey among SMEs to inventory the need for incentives? I.e. bottom-up or are incentives decided top-down? What are the main impediments to development of new orphan medicines by SMEs. Which of these are incentivised? Which of these are still in need of incentives?	Presentation on the EMA SME survey 2020, mentioning challenges faced by SMEs: EMA SME Survey 2020 (europa.eu) Link to the actual survey for more reference: Outcome of SME office survey on the implementation of the SME regulation - Commission Regulation (EC) No 2049/2005 (europa.eu) There will also be a new survey launched soon in the context of the EMA SME office 20-year anniversary, for which there will be a report published once we have the results (in Q1 2025).
Orphan product development strategy has been met with scepticism from founders regarding the amount of data before proceeding to human trials and the absence of profit. How can you support to address these concerns?	If the question is how EMA can ensure that sufficient non-clinical data is available before the development progresses to human, the answer is that we cannot. The approval of clinical trials is done one a national level.
1.3 New pharmaceutical legislation proposal	
Does the agency have any information on the projected timelines for the new EU Orphan Regulation adoption and implementation? The draft EU pharmaceutical reform proposed lower market exclusivity at time of a MAA where 2 year is granted upon launch in all EU markets. This is problematic for advance therapy medicinal products for rare diseases especially reimbursement. How will this be addressed?	The new pharma legislation (NPL) is currently going through legislative procedure and timelines will depend on when co-legislators reach agreement and also the implementation period that will be agreed upon as part of that process. The final text has not yet been agreed on and therefore we are not able to answer detailed questions about the wording of the articles.

Question	Answer
How will you be represented in CHMP if the commission proposal for the pharmaceutical legislation will be followed regarding the reduction of committees? How do you expect the proposed changes in the orphan regulation, reducing the market exclusivity period, will affect the development of new medicines?	
Do you expect to develop any specific regulatory path for very rare diseases in the future?	EMA is currently not aware of any specific regulatory pathways for very rare diseases, they do already fall under the orphan framework.
Guidance of interest on orphan designation development and assessment • The Union Register of Orphan Medicinal Products • EMA public IRIS listing of orphan medicinal product designations • Orphan designation: research and development • Applying for orphan medicinal product designation and requesting pre-submission meeting • Orphanet: knowledge on rare diseases and orphan drugs • PRIME priority medicines • Innovation in medicines • Paediatric medicines: research and development	

2. Scientific advice / protocol assistance

Question	Answer
It would be wonderful if the discussants could address the regulatory roadmap towards approval of re-purposed medications in the rare/orphan diseases space. In particular, what safety data would be required by the EMA for the potential new rare indication and, relatedly, the expectation for efficacy data?	In the case of repurposing, post-marketing experience with the medicine lends support for the safe use of the medicine in the intended indication, but differences in dose, target population, comedications etc. between labelled and new indication may imply the need for additional safety data. On the other hand, efficacy needs to be demonstrated in the new indication and relevant evidence from the literature is often not deemed to be sufficient. Regulatory requirements for a labelled approval tend to exceed those of the scientific or medical community for off-label use and a proper development plan in the new indication would be expected for formal regulatory approval. That said, feasibility issues relating to orphan diseases need to be acknowledged and mechanisms for

Question	Answer
	regulatory approval based on less than comprehensive evidence (marketing authorisation under exceptional circumstances) are in place already.
When would the EMA advise an applicant to go for protocol assistance to discuss significant benefit over competitor product?	Questions on significant benefit can be asked at any timepoint in the development, but they are most meaningful when the overall clinical development plan is being considered, so that the applicant can anticipate which comparisons and in what form would be expected to support such significant benefit conclusion at the time of authorisation. Authorisation of new treatments in the target disease during development may also trigger follow-up significant benefit questions.
What is the role of scientific advice in supporting orphan medicines development?	Scientific advice (called protocol assistance) can be requested for orphan medicines and applicants benefit from fee incentives in requesting it. Scientific advice can cover all areas of the dossier intended to support eventually the marketing authorisation application and it is particularly important for orphan medicines as there is usually lack of published guidance and/or difficulties with conducting a full clinical development in rare conditions. In addition, applicants can ask questions about the evidence requirements to satisfy the criterion of significant benefit against available treatments in order to maintain their orphan designation at the time of authorisation.
Do I have to pay for scientific advice?	Scientific advice is a voluntary and fee-incurring regulatory interaction, but fee incentives apply to orphan medicines which range from 75% fee reduction for orphan medicines from big pharma to full fee waiver for SMEs and academic applicants.
What is the importance of patient representatives and external experts in scientific advice for orphan medicines?	Patient representatives and external experts in rare diseases can complement knowledge gaps and offer unique first-hand insights on the experience of living with and on the management of rare diseases, respectively. These can inform scientific advice in setting the evidentiary requirements and thus optimising development plans for new or existing medicines to be used for rare diseases.

Question	Answer
Not clear enough to me from the discussions the difference of Scientific Advise and Protocol Assistance? Does PA mean the SA for ODD?	Protocol Assistance is indeed scientific advice for orphan designated products. The scope is the same, but in protocol assistance questions on significant benefit can additionally be asked.
Does the protocol assistance of an ODD lead to a kind of fast track if we submit a clinical trial authorisation for a first clinical trial?	Clinical trial authorisation is in the remit of National Competent Authorities and not of the EMA and requirements for clinical trial authorisation are formally different from marketing authorisation requirements. However, clinical trials form part of an overall clinical development programme intended to support marketing authorisation and clinical trial authorisation assessors make use of scientific recommendations made during scientific advice/protocol assistance.
The question on platform technologies - answered was very interesting, did I hear correctly that we can expect guidance but not before 2027?	A proposal for platform technologies has been included in the draft proposal of the new pharma legislation (NPL). The NPL is currently going through legislative procedure and timelines will depend on when co-legislators reach agreement and also the implementation period that will be agreed upon as part of that process.
Do we need to get the orphan designation to get protocol assistance? It takes long time to get the designation.	Protocol assistance is only given to orphan designated products, but scientific advice can be given to any medicinal product development. Orphan designation has a 90-day legal time limit from the start of the procedure to the opinion with an additional 30 days for the European Commission decision.
What type of questions can be asked in the protocol assistance/scientific advice?	Scientific advice/Protocol assistance can cover all areas of the dossier intended to support eventually the marketing authorisation application. In addition, in protocol assistance applicants can ask questions about the evidence requirements to satisfy the criterion of significant benefit against available treatments in order to maintain their orphan designation at the time of authorisation.
How is protocol advice, for companies with ODD and SME status best accomplished? To whom to you address such questions or request for meeting? Understood this may be done outside	The Agency offers assistance to applicants in putting their scientific advice or protocol assistance requests together through preparatory meetings. These meetings are free

Question	Answer
the regular scientific advice pathway, or did I misunderstood?	of charge and held via teleconference. The meeting is requested through the IRIS portal. Preparatory meetings are an opportunity for companies to: - introduce their proposed development programme and receive feedback from Agency staff; - receive feedback on the list of questions to be included in the request for scientific advice, with a view to obtaining satisfactory answers; - identify additional issues to be included in the request for scientific advice; - obtain more detailed information concerning the procedure for obtaining scientific advice or protocol assistance; - ask regulatory questions that are outside the scope of scientific advice; - establish contact with Agency staff involved with the application. The meetings also allow EMA to determine if there is a need for additional expertise at an earlier stage in the procedure. Preparatory meetings are particularly important for first-time users of these procedures, for micro-, small- and medium-sized enterprises (SMEs), and for companies seeking general advice on specific types of medicinal products or therapies.
Guidance of interest on scientific advice and protocol assistance • Scientific advice and protocol assistance • Qualification of novel methodologies for medicine development	

3. Patient engagement

Question	Answer
How can patients contribute to scientific procedures if they do not have any medical/scientific or regulatory experience?	Patients are not expected to have any medical/scientific or regulatory experience. They are invited as experts of living with the condition and its treatment. It is helpful for patients to understand where in the regulatory process they

Question	Answer
	are being invited to contribute and in addition to the support and training offered by EMA, there are some excellent trainings offered by patient organisations.
How can inviting one or two patients be representative of the community?	While one or two patients is not representative of an entire community as we know diseases can be very heterogeneous. The important aspect is to ensure that the patient is part of the conversation and can bring their own personal experience as well as the perspectives of their community (if they are part of an organisation).
What is the added value or impact of patient engagement in regulatory procedures?	Patients have been involved in EMA activities since the creation of the Agency in 1995. Their impact can be seen through the increased number and diversity of activities involving patients at EMA. From membership of scientific committees, participating in scientific meetings, reviewing documents for the public or the creation of the Patients' and Consumer's Working Party (PCWP), there are always new ways of ensuring that the patient voice and perspective is captured at EMA. Regarding the added value, using scientific advice as a case study, we published a paper on The Added Value of Patient Engagement in Early Dialogue at EMA: Scientific Advice as a Case Study. In addition, the most recent methodology to be implemented at EMA involves engaging with stakeholder organisations at the start of marketing authorisation and the outcome report of the pilot (now integrated methodology) is available and demonstrates the added value.
How do you make sure the views of the patients affected by the conditions are represented during the evaluations?	EMA works with a wide network of patient and consumer organisations and they are our first call for identifying individual patients for participation in EMA procedures. EMA is always looking for ways to capture and reflect the input of patients in the different regulatory processes. We interact regularly with our network of organisations and take on board their feedback and suggestions for improved or enhanced patient engagement.

Question	Answer
	The published article The Added Value of Patient Engagement in Early Dialogue at EMA: Scientific Advice as a Case Study demonstrates one way that the views of patients are represented.
Why is the scientific publication of IRDiRC guidebook tool not open access?	Unfortunately, the journal chosen is under paywall. Since this experience, we pay attention to now only publish in Open Access Journals. However, you can access all the materials here: https://orphandrugguide.org/ And the tutorial here: https://www.youtube.com/watch?v=QMJW85VP3Y8
It is still hard for people with health conditions to learn about drugs in development and to collaborate with pharmaceutical companies. This is to protect patients, but do you see ways to make such collaborations easier & more transparent?	Patients frequently belong to patient organisations that often engage with pharmaceutical companies during the development of medicines for their conditions. There are some good trainings available that are organised by patients for patients such as the EURORDIS Open Academy and EUPATI training. While patients don't need to be scientific or medical experts it is helpful to them if they understand the process and timelines and how this impacts them. Regarding making these collaborations transparent, EMA requests disclosure of funding received from pharmaceutical companies when an organisation requests to become an EMA eligible organisation and for individual patients they must complete a Declaration of Interest form before engaging in EMA activities. Patient organisations also have mechanisms in place such as charters and agreements when interacting with the pharmaceutical industry.
Is there any project for collecting real patient data (eg genetic data and phenotypes) in a standardized format? It will incredibly help researchers study all rare diseases we still lack knowledge about molecular-causing mechanisms.	We are currently not ware of a specific project but there is a lot of work ongoing to try and harmonise the way data is collected across Europe. European Platform on Rare Disease Registration | EU RD Platform (europa.eu)
How exactly can patient associations interact with the CHMP?	There are several ways that patients and their organisations can interact with the CHMP.

Question	Answer
	At the start of the marketing authorisation procedure, patient organisations can be contacted to submit their feedback (see outcome report) that is shared with the CHMP rapporteurs at the early stage of the assessment. Later individual patients can be invited to participate in Scientific Advisory Groups or in oral explanations with the company.

Guidance of interest on patient engagement

- EURORDIS umbrella of patient organisations
- IRDiRC orphan drug development guide and the tutorial
- Further reading from IRDiRC: Targeting shared molecular etiologies to accelerate drug development for rare diseases
- Individual patients and patient organisations interested in collaborating with EMA can find information on how to do this on this page: Getting involved
- The Added Value of Patient Engagement in Early Dialogue at EMA: Scientific Advice as a Case Study
- About ERNs and patient involved in these networks
- Read about stakeholder engagement in these reports
- Recommendations from the Rare 2030 foresight study mentioned (including some suggestions around improving access for PLWRD)

4. Academic developers

Question	Answer
As researchers, we are encouraged to contact the EMA at an early stage of development. What is the best moment to start interaction, and do we need to have an Orphan Designation for it?	It is convenient to request a first early contact by writing to academia@ema.europa.eu. This interaction will be most useful when you are considering aligning your research with regulatory requirements in view of either adding value and impact to your research strategy, valorising your research results for tech transfer, or understanding the different options for regulatory development on the basis of your results/design. It can be at the pre-clinical stage or later (the earlier the better for alignment and sustainability) and you do not need to have an orphan designation previously. You can also contact us to request consideration for participation in your research project if you

Question	Answer
	think you fulfil our criteria. Do this by writing to regulatory.science@ema.europa.eu
I am an academic researcher developing an advanced therapy for a rare disease. Is there a specific point of contact or shall I write to the orphan drug department or to the advance therapies department?	Ideally, please contact us first by writing to academia@ema.europa.eu and we will advise you on which regulatory path would be more advantageous for you to take on the basis of the data you have.
Are there any insights on the engagement from SMEs and academia in the development of orphan medicines? It can be overwhelming for academia to pursue development	We recommend that you align your research with regulatory requirements early in order to reduce industry's risk perception of your results and leverage tech transfer activities. In a failed market situation, where for-profit industry cannot be interested in your development, we recommend you come and speak with us about your hurdles and needs by writing to academia@ema.europa.eu as it will help us thinking of future solutions to address your needs.
Guidance of interest for academic developers • Information on the European Medicines Agency's activities that are most relevant to academia • Regulatory Science Research Needs • ATMP pilot for academia and non-profit organisations • Guides for regulatory development of ATMPs • ITF Briefing meeting	

5. Clinical methodology

Question	Answer
What are the specific methodological considerations for small population in clinical trials	The general principles relevant for small populations are outlined in dedicated Guideline. It can be found here, note that the website contains also links to other, related topics. Note also one point from its summary: " There are no special methods for designing, carrying out or analysing clinical trials in small populations. There are, however, approaches to increase the efficiency of clinical trials. The need for statistical efficiency should be weighed against the need for clinically relevant/interpretable results; the latter being the most important."

Question	Answer
Would you be able to suggest any reference/are there any workshops planned on innovative trial designs e.g. testing potential new drug candidates addressing same metabolic pathway?	As general comment (irrespective of metabolic pathways): There is the ACT EU initiative which aims at accelerating and improving the Clinical trial landscape in Europe. Part of the work is also to organise workshops. There was a recent workshop at the end of last year on Clinical Trial methodologies (incl. Innovative designs) and another one on a broader level on the set-up of the Multi-stakeholder platform. There are also a number of workshops organised by learned societies or trade unions where EMA colleagues regularly attend and/or present.
Do you see any innovations (AI, data twins, EMR) that offer near term changes on how clinical trials are done, to reduce the data quantity threshold required for approval, while ensuring safety and proof of evidence?	No near-future changes are currently foreseen. Assessing results generated on data based on small populations is already challenging. Hence, further reducing data and especially the sample size would not seem appropriate. 'Digital twins' is a concept that is used to create a digital simulation of a physical object to explore how it behaves under varying conditions. AI/ML can be utilized to build in silico representations or replicas of an individual that can dynamically reflect molecular and physiological status over time. So far, it has not been sufficiently demonstrated that digital twins can contribute to the evidence needed for regulatory decision making. In general, Artificial Intelligence (AI) and Machine Learning (ML) tools have the potential to effectively support the acquisition, transformation, analysis, and interpretation of data across the medicinal product lifecycle. Their application can include, for example, AI/ML modelling approaches to replace, reduce, and refine the use of animal models during the preclinical development. In clinical trials, AI/ML systems may support the selection of patients based on certain disease characteristics or other clinical parameters; AI/ML tools can also support data recording and analyses which will in turn be submitted to regulators in marketing-authorisation procedures. In this fast-moving field, EMA has published a draft reflection paper outlining the current thinking on the use of AI to support the safe and effective development,

Question	Answer
	regulation and use of human and veterinary medicines.
Would it be possible to get more insights on indirect comparison of ODD significant benefit?	There is not yet a dedicated EMA guideline that describes statistical methodology for significant benefit. A number of methods has been described in the scientific literature. The EUnetHTA21 initiative has published this document on indirect comparisons and the NICE DSU has also a list of technical documents relevant for their work. Although the aforementioned documents cannot be understood as official guidance documents of the EMA, they might serve as a starting point for understanding the strength and limitations of different methods.
Guidance of interest on clinical methodology • General principles for trials in rare diseases are outlined here. • An overview of biostatistics guidance documents can be found here.	

6. European Commission funded research

Question	Answer
Can companies developing orphan drugs join EU-funded research projects?"	Yes, companies can join collaborative consortia applying for EU research and innovation funding. It is visible, with all partners being listed for each EU-funded project, in the cordis database of funded projects. Not only companies developing orphan drugs, also companies with different profiles are involved in EU-funded research projects, for example companies developing diagnostic methods, working on tools, technologies etc. Also the public-private Joint Undertaking "Innovative Health Initiative" (IHI), providing funding from Horizon Europe and industry involvement, is an opportunity for companies to be involved in collaborative research projects at EU level, in a pre-competitive space.
Commission's involvement regarding funding in terms of what they do and how they work?	The Commission is on one hand, with the support of executive agencies, managing and implementing the different schemes available under the EU research and innovation

Question	Answer
	framework programmes (FP7, Horizon 2020, Horizon Europe) and on the other hand proposing and drafting future call topics, in close cooperation with Member States' representatives (Programme Committee, configurations specific to the different clusters: for example Health Cluster for health research). The Commission is also following EU-funded projects and steering in particular flagship initiatives which enhance and frame specific ecosystems, such as, for the field of rare diseases research, the European Joint Programme co-fund on Rare Diseases (EJP RD 2019-2024) under Horizon 2020 and the future European Partnership on Rare Diseases under Horizon Europe. Other, more 'bottom-up' schemes such as grants from the European Research Council (ERC), the European Innovation Council (EIC) or Marie-Slodowska-Curie-Actions (MSCAs) are also available to all researchers including rare diseases researchers.
What type of funding is or will be available in the rare disease space?	The main flagship initiative in the field of rare diseases research in the next years will be the European Partnership on Rare Diseases (ERDERA proposal submitted in September 2023, starting in September 2024, there will be further "joint transnational calls" for rare diseases researchers), while other call topics can also serve different needs of the rare diseases community, keeping in mind that rare diseases teams do not necessarily need to answer to rare diseases-specific calls. Horizon Europe will still have two work programmes: one for 2025 and one for 2026-2027, thus call topics under the Health cluster (for health research) will be visible in these work programmes, before becoming accessible for application via the Funding portal. Grants from the European Research Council (ERC), the European Innovation Council (EIC) or Marie-Slodowska-Curie-Actions (MSCAs) also remain interesting opportunities.
Following on the comment from EC representative on European networks, would be great to apply it to clinical trials and facilitate	The new Clinical Trial Regulation harmonising rules of clinical trials in the European Union, fully entering into force in 2025, should facilitate the

Question	Answer
cross boarder participation (patients traveling abroad for clinical trials)	implementation of clinical trials and also improve transparency in the landscape of clinical. Indeed for rare diseases patients, involvement in clinical trials could also be facilitated thanks to the existence of and active research efforts of the 24 European Reference Networks (ERNs). The EU-funded research project ERICA is exactly meant to support research efforts of ERNs such as clinical trial readiness (with Work Package 4 on clinical trial support).
Most orphan diseases manifest in childhood, and the curative potential might be highest in earlier years. Do you have ideas on how to incentivise even more strongly the development of treatments for children? E.g. through value-based models	Several initiatives were already launched to incentivise and further support the development of treatments for children, such as the public-private project "Conect4Children: Collaborative network for European clinical trials for children" (C4C) funded under IHI Joint Undertaking. For continued efforts, C4C project has created a legal entity which is planned to be a partner within the upcoming European Partnership on Rare Diseases (ERDERA proposal) to start in September 2024, thus efforts to incentivise the development of treatments for children will be further pursued, also along the new Pharmaceutical Package.
Do you expect to develop any specific regulatory path for compassionate use programmes for rare diseases in the future (more than Reg. 726)?	Compassionate use will remain as today a possibility, under certain conditions for member states.
Do you think that changes and restrictions proposed by GPL especially to the incentives in EU (reduction of ME) could have a negative impact on the R&D in EU and to the availability of new treatments for EU patients in rare space?	No, at the contrary the changes in proposed in the revision of the pharmaceutical legislation are expected to increase the research and development on rare diseases in particular in areas currently underserved or where the available treatment options are not optimal. The reform include a modulate (but still higher than the one proposed for example in the US where the ME is of 7 years) ME with an higher reward for products addressing the high unmet needs of patients. In addition regulatory and scientific support by Ema will help in the early phase of development of medicines for rare diseases. Furthermore they provisions included in the proposal are expected to improve timely access

Question	Answer
	to innovative medicinal products for all patients in the EU.

Guidance of interest on EC funded research

- Examples of 11 EU-funded research projects (possibly grouping rare diseases)
- Research on Rare Diseases at EU level
- European Reference Networks
- Cordis database of EU-funded research projects
- European Joint Programme co-funded on Rare Diseases (EJP RD, 2019-2024): https://www.ejprarediseases.org/; https://cordis.europa.eu/project/id/825575
- Future European Partnership on Rare Diseases (ERDERA proposal, meant to start in Sept. 2024): https://www.ejprarediseases.org/erdera/; https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/horizon-hlth-2023-disease-07-01
- Coordination and Support Action for enhancing clinical research of ERNs, ERICA: https://erica-rd.eu/; Work package 4 on Clinical Trial support: https://erica-rd.eu/work-packages/clinical-trial-support/
- Innovative Health Initiative (IHI) Joint undertaking (public-private cooperation, with Horizon Europe funding and industry involvement)
- Example recent IHI call relating to rare diseases 'Establishing novel approaches to improve clinical trials for rare and ultra-rare diseases'
- IHI project "Conect4Children" (C4C): https://cordis.europa.eu/project/id/777389; https://www.imi.europa.eu/projects-results/project-factsheets/c4c
- Clinical Trials Regulation

7. Contact Points

- Support to SMEs and contact point sme@ema.europa.eu
- Contact point for academic developers: academia@ema.europa.eu
- Send a question to the European Medicines Agency | European Medicines Agency (europa.eu)