Support for development of orphan medicines

Report from EMA workshop held for early medicine developers in the area of rare diseases

Introduction

Year 2020 marked the 20th anniversary of the introduction of the Orphan Regulation in the European Union and which coincided also with its evaluation by the European Commission. Despite objective successes of the Orphan Regulation, many disease areas have still not attracted sufficient attention and need more dedicated research.

This workshop was set up to encourage early and efficient interactions with the regulators by highlighting pre-marketing support for medicine development in rare diseases. Existing tools such as orphan designation, protocol assistance and PRIME scheme were presented in the context of early product development strategy. Furthermore, the Committee for Orphan Medical Products (COMP) explained key elements essential for a successful orphan designation application.

Stakeholders had an opportunity to express their views in relation to early medicine development and regulatory interactions and to participate in related Q&A sessions. Questions that have not been answered during these sessions because of time limitations are covered at the end of this document.

The workshop was targeted at small to medium enterprise medicine developers, academia, patients, healthcare professionals and ERNs who are often at the forefront of medicine development in rare and neglected diseases. The workshop was chaired by the Chair of the Committee of Orphan Medicinal Products (COMP) – Prof. Violeta Stoyanova-Beninska. EMA's Michael Berntgen, the head of Scientific Evidence Generation Department, provided opening and closing remarks.

Session 1 – Orphan Development Support

The workshop started with an overview of the orphan regulation and related guidance documents published by the European Commission and EMA.

Dr Frauke Naumann-Winter and Darius Matusevicius of the COMP explained the four criteria for orphan designation. These include the eligibility of the condition as a chronically debilitating or life threatening and rare (affecting under 5 in 10,000 patients in the EU) disease, demonstration of product development specifically for the applied condition and fulfilment of significant benefit, should another product be already authorised for the proposed condition. The criteria are assessed by the COMP, which is composed of delegates from all EU members states and 3 patient representatives. All criteria for the initial orphan designation must be confirmed at the time of marketing authorisation during the orphan designation maintenance procedure. Dr Naumann-Winter also presented some statistics to illustrate the gap between the estimate number of rare- conditions and the number of orphan products

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– and expressed the hope that scientific community, represented mostly by academic and SME participants of the workshop, could in the future help address this gap.

Dr Darius Matusevicius explained that assessment of each application starts with the acceptability of the condition. Provided that the condition is also rare and chronically debilitating, further data is assessed. Reference was made to COMP publication, which may help in defining what constitutes a valid condition acceptable for a designation. Dr Matusevicius underlined the importance of the quality of submission, including the necessity of submitting well reported and designed study results in support of medical plausibility and significant benefit. The need for in vivo data in a relevant model of the condition, or for preliminary clinical data was expressed. Dr Matusevicius explained also the instances when prevalence or incidence of the disease are expected in the submission, and the importance of adequate presentation of data in this part of the application. Finally, the criterion of significant benefit was explained, which may refer to clinically relevant advantage or major contribution to patient care. The level of evidence for each claim was discussed and illustrated by examples. The last slide of the presentation contains references to all relevant publications regarding the criteria assessment by the COMP (please see also the bibliography of this document).

Helene Casaert and Rosan Vegter provided information on the services offered by the SME office and the academic liaison at the EMA to those seeking further incentives on account of their SME/academic status. Helene Casaert made reference to the SME regulation, which has been in place for 15 years. Based on the SME regulation, the SME office at EMA was created to provide an entry point for regulatory interaction. The first step in such interaction is an application for an SME status at EMA. Depending on the size of the company, incentives may vary. Therefore, a formal registration is important. Helene Casaert provided also an overview of questions that may be addressed by the SME office. Similar support is available for academic stakeholders via the Academic Liaison office at EMA. Question that can be asked can be related to Innovation Task Force (ITF), PRIME scheme and orphan designation scheme, protocol assistance or scientific advice, and free of charge advice on the regulatory strategy customised to the company's needs. An overview of incentives, and types of help provided to SMEs and academics, was described. It was recommended that the SMEs look for guidance, which is abundant at the EMA corporate website, and to come to EMA early and often to support product development and pave the way to a successful marketing authorisation.

Virginie Hivert presented the recently developed International Rare Diseases Consortium (IRDiRC) Orphan Drug Development Guidebook, which is a rich source of regulatory, scientific and methodology information relevant for many orphan medicine developers. Ms Hivert introduced the history of the project, which stems from the recognition of the unmet need in the area of rare diseases and the ambitious goals of the IRDiRC to develop 200 diagnostic tools for rare disease until 2020 and 1000 new therapies by 2027. The Guidebook provides a structured and standardised framework, which will help organise and optimise the use of the multitude of tools available for the development of orphan drugs. All types of medicine developers can make use of this toolbox and the specific needs related to different types of medicines has been included in the framework. This applies to standard medicines, advanced therapies and medicines for so called disregarded diseases, of which limited knowledge exists. The results of this work by IRDiRC have been published and the Guidebook itself can be found at: https://orphandrugguide.org/.

The session ended with a brief question and answer session chaired by the COMP member from Denmark, Dr Elisabeth Penninga. Any questions posed to the speakers during this session are included at the end of this document.

Session 2 – Pre-marketing incentives for development in rare diseases

Prof. Armando Magrelli provided an overview of scientific advice which is specific to orphan products and termed 'protocol assistance'. Prof. Magrelli advocated, based on examples from years of experience of the scientific advice at EMA, for sponsors to come and interact with regulators early. This may allow for flexibility of the medicine development plan and to use the full spectrum of advice available. This includes questions on non-clinical, clinical data, quality, qualification of biomarkers, or post-marketing plans. There's also a possibility of parallel advice involving HTA bodies or regulators from EMA and FDA together. Recipients of orphan designation benefit from fee incentives and can address specific questions to the COMP regarding the maintenance of the orphan designation. The PRIME scheme was presented in terms of eligibility criteria and resulting incentives. The scheme allows for proactive and reiterative scientific advice which may help steer and accelerate the development of the product towards the unmet medical need. Timely eligibility requests were again recommended to optimise the benefits of this scheme for both, developers and patients.

Dr Daria Julkowska of the European Joint Programme on Rare Diseases (EJP RD) presented an overview of all existing and planned funding schemes related to research and development in the rare disease area. The objective of the EJR RD are to bring all types of stakeholders together and to provide a common platform to facilitate rare disease research. About 130 institutions from 35 countries participate in EJP RD, which covers the majority of the European rare disease community. The structure of EJP RD was presented. The Joint Transnational Call, an annual funding scheme of EJP RD was outlined together with eligibility criteria. The current call (deadline 22 Feb 2021) is the first multinational call for social sciences and humanities, which includes a very broad range of research of rare diseases. Further, the EJP RD internal call for innovative methodologies is also launched to improve the research and development in the area of rare diseases. Other types of support include the Networking Support Scheme, Research Mobility Fellowship and Research Training Workshop funding. EJP RD offers also an array of training opportunities which can be found on the website and are free of charge. Lastly, EJP RD is involved in facilitating multi-stakeholder partnerships though other initiatives such as supporting mentoring programs and development platforms (such as the IRDiRC Orphan Guidebook). Lastly, the Clinical Trials Support office of EJP RD, focused mainly on academic trials that need support, pair the developers with a pool of mentors who can help with additional advice in the course of clinical development. Funding schemes which aren't specific to rare diseases, such as Marie Curie Fellowships, were also highlighted as potentially very interesting and attractive for anyone who develops a research topic and seeks out research collaborations in drug development.

The session ended with a brief question and answer session chaired by the Head of the Orphan Medicines Office at EMA, Ms Kristina Larsson. Any questions posed to the speakers during this session are included at the end of this document.

Session 3 – Stakeholder's perspectives on the value of orphan designation

The session was opened by Dr Juan Antonio Bueren who spoke on behalf of CIBERER, a Spanish academic organisation well experienced in obtaining orphan designations and protocol assistance for development of medicines in rare haematological condition, such as Fanconi anaemia. CIBERER is an academic consortium which fosters research in rare diseases. Products developed by members of CIBERER, that received orphan designations, include repurposed drugs and advanced therapies. Dr Bueren highlighted the positive aspect of holding an OD, which is an affordable way to boost the status of one's research. Obtaining OD increases the visibility of one's research to other stakeholders, opens

access to orphan specific funding (nationally and EU wide), protocol assistance as well promotes development of industry-academia collaborations thanks to this regulatory support. In critical remarks, Dr Bueren highlighted that some academics may be still struggling with putting together OD applications mainly due to limited resources to in depth epidemiology research (needed to establish the prevalence of the intended condition). It was proposed that more information in the public domain about previously accepted prevalence calculations and sources would be helpful to alleviate this burden. It was also proposed to simplify the process of prevalence estimate evaluation in disease that are clearly rare (below the limit of 5 in 10,000). Dr Bueren presented an example of a successful application for treatment of Fanconi anaemia. The achievement of an orphan designation opened the eligibility for a national orphan specific funding call and many other incentives both nationally and internationally. Additionally, opportunity to build regulatory knowledge and initiating cooperation with industry stakeholders hold an opportunity for the academic researchers in rare diseases.

Next, the presentation of Dr Andrea Braun-Scherhag, who spoke on behalf of EUCOPE, brought the perspective of European small to medium enterprises (SMEs). Dr Braun-Scherhag provided an overview of the extent of development in the area of rare diseases. She praised the orphan regulation for achieving a great deal of success since its implementation 20 years ago with over 140 orphan medicines already placed on the market. That said, rare diseases are often not very well described in the literature and often from the wrong perspective. This is particularly challenging for ultrarare diseases. In discussing incentives and support for SMEs, Dr Braun-Scherhag highlighted dealing with a rare disease this brings unique challenges. Orphan designation was found of high value both for SMEs and for the investors, who count on the fast medicine development. The centralised process that is harmonised across the EU was also found of value. The incentives are naturally also of value, especially with key importance of the 10 years of market exclusivity. Dr Braun-Scherhag encouraged the developers to interact with the regulators early on in development in order to help make difficult decisions (such as the choice of endpoints) and to satisfy regulatory requirements. Among challenges, several points were raised, including the evolving standards of the COMP in evaluating application and perceived misalignment between the requirements of various regulatory committees (globally) and between paediatric development requirements in various orphan conditions. In view of the ultrarare nature of some diseases and the need for single arm studies, it was seen as important to come to an agreement about the regulatory acceptability of the real-world evidence as source of comparative data. Due to heterogeneity of many rare diseases, it was considered necessary to agree on, and further develop, the use of patient reported outcomes, which may be more universally applicable than many of the clinical endpoints. Support for the European Reference Networks and for the integrated pathway for device and orphan medicine combination products were also highlighted as elements that could foster development of orphan medicines. And lastly, it was considered important that the HTA should understand the orphan framework requirements, which to a degree may overlap with their own.

In the questions and answers session Dr Braun-Scherhag also expressed an opinion that taking a step to apply for an orphan designation is indicative of a major commitment and that this may be the reason why many diseases are still neglected. In view of the evaluation of the orphan regulation by the European Commission, it is also possible that the stakeholders lack confidence about the stability and the future of the orphan framework in Europe.

Last but not least, the perspective of patients was delivered by Nick Sireau, the CEO of the patient organisation AKU, representing patients with alkaptonuria. AKU is the only patient organisation in Europe which successfully utilised the orphan designation of a product covered by their advocacy to build a network of experts, obtain the funding and bring the product (nitisinone) to the market. The story of nitisinone demonstrates that also patient organisations may utilise the incentives of an orphan designation to further the development of a promising product. Patients contribution to development of study protocols can also be especially valuable in the area of rare diseases, where selection of

endpoints and patient recruitment may pose challenges. Mr Sireau used the example of nitisinone to highlight many advantages of the European orphan framework and obtaining and orphan designation. Mr Sireau identified the difficulties in developing this medicine and highlighted the good will of the pharmaceutical company to invest in the development despite funding challenges. Forming an international network of collaboration helped identifying patients who could be recruited into the clinical study, which often is so challenging in the rare disease area.

The session ended with a brief question and answer session chaired by a member of the Orphan Medicines Office at EMA, Dr Maria Sheean. Question posed to the speakers by the external audience during this session are included at the end of this document.

IRIS Clinic

Following the main part of the workshop Dr Paolo Tomasi of EMA provided an introduction to registration of an applicant using EMA's IT systems, and most notably, the IRIS platform. Further guidance on this topic can be found at: https://www.ema.europa.eu/en/events/online-training-how-register-access-iris

Conclusions

In conclusion, the workshop was met with a broad interest from many stakeholders, who attended the event via broadcast. The event covered a broad range of topics related to orphan medicine development and to support for early medicine developers, such as academics and SMEs.

Medicine developers were invited to start their interactions with the regulators early and to seek advice on the more efficient and targeted use of support measures offered by EMA and other regulators. Similarly, the presentations on IRDiRC Orphan Drug Development Guidebook and EJP RD funding schemes highlighted the multitude of options where developers can find support and the importance of cooperation in this challenging area of orphan drug development.

In her closing remarks, Prof. Stoyanova acknowledged the fact that despite clear appreciation for the incentives granted by the orphan scheme in Europe, more work can be done to support applicants in obtaining orphan designations. This could include publication of recent prevalence calculations to aid the applicants with limited resources to study epidemiology.

More broadly speaking, understanding the disease was raised by many speakers as pivotal for even starting to think about medicine development. As such, it was noted that 'speaking the same language' would help bring stakeholders together in understanding rare diseases. It was agreed by most speakers that support for collaborating, networking and early regulatory interactions may be helpful.

As the EMA organised the event not only to provide guidance to the audience but also to learn from all invited stakeholders, the tips and suggestions from CIBERER, EUCOPE and AKU were very much appreciated. The highlighted needs of the research community in rare diseases will feed into further regulatory discussions in order to achieve the goal of stimulating medicine development for rare and neglected (or disregarded) diseases.

Questions and Answers

Orphan designation

Is orphan designation for known drug products/established products for new indications supported?

Yes. Development of known products in new indications is supported.

Is it possible for a designated orphan medicine to become an authorised orphan medicine, and if so, what are the advantages for the MAH?

An orphan designated medicine can become authorised if the criteria for orphan designation are maintained at the time of marketing authorisation. There are marketing authorisation fee reductions foreseen for orphan designated medicines. Once authorised, orphan medicines are entitled to 10 years market exclusivity.

What would be the minimum data expected to be submitted in support of the ODD submission? Are in vitro proof of concept data sufficient, e.g. for an ATMP/GTMP?

The COMP assesses the medical plausibility and the significant benefit of the proposed product over any other authorised products for the proposed condition. If there are no other products authorised for the proposed condition, the minimum data required by the COMP is usually in vivo data in a model of the proposed condition. Appropriate measures of activity are expected, which could indicate an effect relevant from the clinical standpoint (e.g. functional endpoint such as disease symptom alleviation, improved survival, motor function, behavioural improvement etc.).

Is there a list of diseases that are already defined as "orphan", (i.e. the sponsor does not have to provide a prevalence justification) e.g. pancreatic cancer?

The list of conditions accepted by the COMP in the recent past can be checked in the EC Community Register of Orphan Medicinal Products. Conditions in older designations may have changed because of the evolution of the COMP standards in designating conditions or because of the evolution of classification of diseases in the scientific community.
The prevalence must be submitted with every application because this is a changing variable. It may change as a result of increased disease incidence or because of improvements in disease diagnosis or management. The latter may impact patient survival. Therefore, an up to date (as far as possible) reporting of disease prevalence is expected.

Which is the preferred source for evaluating the prevalence of a condition?

Disease national and international registries, community databases and primary epidemiological studies are preferred. Peer reviewed literature reporting disease incidence or prevalence can be accepted in absence of other sources. In many cases, indirect methods of calculation have to be employed. For the estimation and presentation of the prevalence estimate please to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

How can one show the prevalence of a condition in the EU, if no (complete/EU wide) registry is available?

In absence of registries, other sources of primary epidemiological data are acceptable (see previous question).

Could publications related to different area of the world than EU be used for the prevalence in the ODD application or just publications related to EU?

Where there is very little information available on the incidence or prevalence of the condition from European sources, non-EU data can be used as supportive evidence. It is useful to discuss in such cases, if the prevalence of the condition is expected to be varying across the globe e.g. due to ethnic differences.

How can we know the prevalence when a lot of rare diseases are underdiagnosed?

The COMP accepts the calculation of prevalence based on the number of diagnosed cases. Estimates of underdiagnosed cases are not considered relevant because undiagnosed patients will not be treated.

Is orphan drug designation expiry (10-12 years from the designation) always applied? is the owner informed and how?

The removal of the product from the Orphan Medicinal Product Register is always triggered upon the expiry of the market exclusivity period. The marketing authorisation holder is not informed of this step. However, it is clear from the EC registry website at what exact date the exclusivity expires.

Are the 3 patient representatives in the COMP permanently appointed or do they vary dependent on assessed orphan drug?

The 3 patient representatives are appointed for a period of 3 years just like all other members of the committee. Their appointment can be renewed. They are familiar with the COMP mission and assist with all orphan designation applications. Should the COMP require specific input relating to a particular condition, additional patient representatives with expertise in that condition can be invited to the plenary. This usually happens at the time of maintenance of orphan status at the time of marketing authorisation.

If an indication initially granted orphan designation is expanded after MAA approval (larger patient population), what happens to the 10-year exclusivity?

If at the time of extension of indication, the population covered by the therapeutic indication is broader, a new maintenance report has to be submitted to demonstrate that the criteria for an orphan designation are still met. If the new population is covered by the existing orphan designation and the criterion of significant benefit and prevalence are still met, the product maintains its market exclusivity. However, if one of criteria is no longer met or the extension involves a population not covered by an existing orphan designation, the product must be withdrawn from the orphan register and the market exclusivity is terminated. The product may, however, stay on the market as non-orphan.

Is it possible to apply for more than one orphan indication for the same medicinal product?

Yes, new orphan designations in new conditions can be applied for as long as there is supporting data specific for the proposed new condition with the proposed product.

There is an increased harmonisation with the FDA. I believe that they use a figure of less than 200.000 rather than 5 in 10.000 in the EU?

There are several differences between orphan frameworks in the EU and USA. With regards to prevalence, the ceiling of orphan eligibility is less than 200.000 patients in USA (an absolute number) and number of less than 5 in 10.000 persons in the EU (a proportion). Further information about both frameworks can be found:
EMA: https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview
FDA: https://www.fda.gov/industry/developing-products-rare-diseases-conditions

If an orphan medicinal product OMP works for a subset of the designated population (biomarker+), does the developer need to demonstrate the product has no effect in biomarker neg. patients?

The COMP designates conditions, which are usually broader than the target population for which a positive benefit/risk balance can be demonstrated. Therefore, as long as the broad condition meets the prevalence criterion, the evidence of efficacy in the condition does not have to cover the entire included population.

If a drug is used to prevent a symptom of the disease, would we pursue a "treatment" or "prevention" orphan designation?

Prevention of a symptom is understood by the COMP as 'secondary prevention', which is included in broadly understood treatment of the condition. Therefore, the application should be phrased as 'treatment of the condition'.

Has EMA become more stringent over the latest years in reviewing orphan similarity and the maintenance of the OD at the time of MA?

The criteria for orphan similarity have not changed in the recent years. Further can be found at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/orphan-medicines/applying-marketing-authorisation-orphan-medicines#orphan-similarity-section

The criteria for maintenance of the OD at the time of MA have not changed. However, since the publication of The EC Notice on the implementation of the orphan regulation 2016 (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2016_424_R_0003&from=EN), the step of maintenance of the OD was also introduced for extensions of indications to new patient populations within an already approved orphan condition.

Regarding the medical plausibility is there an obligation to submit all clinical efficacy data up until that moment (e.g. phase 1 data) or can you use a selection?

The sponsor is encouraged to accurately report the stage of product development at the time of initial orphan designation. Only the most relevant data (data in patients affected by the proposed condition) is expected in the medical plausibility and significant benefit sections of the application. Any additional data can be added in section E1 of the application and in form of an annex (e.g. as attached Investigator's Brochure).

What kind of support does EMA (and other agencies) offer in preparing the ODD for EU but also non-EU countries? Is there e.g. a template available?

The guidance on application for orphan designation is published on EMA public website: https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/applying-orphan-designation

The Orphan Medicines Office at EMA offers also pre-submission meetings which can help the applicant improve the quality of their submissions.

For any further questions please refer to the questions section of the EMA website:

For a biosimilar OMP, does the applicant need to demonstrate superiority in a phase III trial?

If a product is indeed biosimilar, it would most likely be assessed as 'similar' to an existing orphan medicine under protection of market exclusivity. In such case, the product would have to demonstrate clinical superiority over the originator. However, if the market exclusivity of the originator has already expired, the biosimilar would not have to demonstrate superiority any longer.

What is the committee's take on orphan drug designation for tissue agnostic diseases?

So far, no tissue agnostic indication has been granted orphan designation to date. Instead, to date it was found more justified to designate the underlying diseases, which are well defined and described in scientific literature. Further reflections of the COMP on biomarker driven indications can be found in this article.

What should the SME keep in mind while preparing an ODA for tumour agnostic rare disease?

Please, see the answer above.

If the only available treatment for a disease is surgery, do we also need to show significant benefit over surgery for an orphan drug?

All therapeutic options should be described in the application. However, if there is a subpopulation affected by the condition for which surgery is not an option or is not curative, no justification of significant benefit has to be provided. Instead, the sponsor would be required to describe the population for whom the proposed product would be most beneficial.

Please elaborate on conditions that have low prevalence but may be higher than the orphan threshold where the application is based on non-return-on-investment claim.

Demonstration of non-return-on-investment has proven very challenging as a basis for orphan designation. Only one such application was successful since the foundation of the regulation. This is, among others, because it is difficult to ascertain the price of the product once on the market. It is also challenging to estimate the difference that all pre- and post-marketing incentives would bring should the product be awarded an orphan designation. With regards to the condition, the prevalence criterion does not apply, however the number of patients affected by the condition would still have to be provided. All other rules of defining a condition as seen by the scientific community would still apply.

Does EMA provide a scientific advice on comparators to demonstrate significant benefit, especially for conditions where comparators may not be the same in US and EU?

A sponsor can seek protocol assistance on development of an orphan designated product. Within protocol assistance, the sponsor can ask a question directed to the COMP to make sure that the sponsor's plan for the demonstration of significant benefit is agreed on. This includes the choice of comparators. Of note, for the demonstration of significant benefit, only products authorised in the EU (on national or central level) are taken into consideration.

What is the percentage of ODs based on major contribution to patient care?

In the year 2020, of all initial designations, 64% had the requirement of significant benefit, and none were based on the claim of major contribution to patient care. In 2019, 3% of initial designations with significant benefit were based on major contribution to patient care.

Is the "significant benefit" an exclusive EMA requirement and FDA doesn't require it?

Indeed, the US orphan drug act does not stipulate the demonstration of significant benefit.

Could you tell us a bit more about how an OD could be designated based on the incidence solely?

In cases where the condition is known to be contained within one year of duration (as is in case of many infectious diseases), annual incidence can be accepted by the COMP as equal to the prevalence of the condition. In these cases, only submission of annual incidence will be required.

What percentage of orphan drug applications are successful? Are there lessons learned that can be shared to improve the chances?

In the year 2020, around 64% of applications were successful and this is in line with success rate in previous years. In order to succeed, it is recommended to seek information and follow guidance published on the EMA website:
https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview

Additionally, publications authored by members of the COMP, often shed light on how criteria for an orphan designation are applied. The list of recommended literature can be found at the bottom of this document.

In case a product is intended for the use in 2 separate orphan designated conditions, is it possible to have a single protocol assistance (PA)?

Yes, if all populations covered by PA in also covered by existing orphan designations, the advice can be merged.

OD is re-evaluated during MAA. Is there a possibility to maintain the OD designation if there is already approved orphan drug product in the same indication?

Yes, it is possible to maintain orphan status as long as the new product demonstrates significant benefit over the existing medicinal products for the same condition. More on the concept of significant benefit can be found at: DOI: 10.1016/j.drudis.2017.09.010

What consideration should be taken into the account in order to be eligible to maintain the OD?

It is highly recommended to watch the space of intended therapeutic indication. In the event of another product coming to the market, appropriate preparation for the demonstration of significant benefit should be undertaken. This may include the protocol assistance and a consultation with the COMP on the topic of significant benefit. At the time of MAA, timely submission of a Maintenance Report is also recommended. For more information see: https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview#marketing-authorisation-stage-section

Who is responsible for the post-marketing monitoring of orphan medicines authorised with conditional approval or other special MA procedures?

In terms of products receiving conditional MA or MA under exceptional circumstances, no difference exists between monitoring of orphan and non-orphan products. Any post-authorisation studies will be assessed by CHMP/CAT and PRAC as agreed at the time of the initial MAA.

Is it possible to get 2 different ODDs and subsequent MAs for the same product in different indications, achieving 2 independent orphan exclusivity timeframes?

Yes, it is possible to obtain a marketing authorisation for one product, for which the therapeutic indication is covered by more than 1 orphan designation. This can result in separate periods of market exclusivity if e.g. a second population covered by a second orphan designation has been added during an extension of indication.

Is it possible to get an orphan drug designation for a non-clinical candidate? (i.e. just a lead antibody candidate that is still to be optimised)

It is possible to obtain an orphan designation for a candidate product as long as the changes are well defined and are not expected to alter the product's potential to show activity in the proposed condition. For example, data with the use of mouse specific antibody has been previously accepted in support of an application for a humanised version of that antibody. Other differences between the prototype product and the intended final product would be discussed on a case by case basis when deciding on the acceptability of bridging data from early non-clinical data.

What is the difference between the condition and the indication in the ODD application?

The orphan condition is defined in the orphan regulation and existing guidance documents. It exists independent of the pharmacodynamic properties of the product and benefit /risk considerations. The condition is usually described in the scientific and medical literature based on defined aetiology, histopathology, pathophysiology, clinical characteristics and as much as possible classification systems. In contrast, therapeutic indication is a well-defined patient population, often smaller than this affected by the broader orphan condition, for which a positive benefit /risk balance was determined by the assessing committee (e.g. CHMP at EMA).

The marketing exclusivity for orphan drug is 10 years, while that for other new non-orphan drugs is also 8+2 years, what are the differences between these?

The market exclusivity granted for orphan medicines relates to the 10-year period after the marketing authorisation of an orphan medicine when similar medicines for the same indication cannot be placed on the market. Market exclusivity can be extended to 12 years if the paediatric investigation plan is completed.
Non-orphan medicines are covered by data protection (8+2 years) and market protection (10 years) only. For further information related to the definitions of data exclusivity, data protection and market exclusivity, please go to the presentation on the EMA website.

Is a PIP mandatory for an extension application of orphan MA under well-established use if the extension doesn't apply to a change in therapeutic indication?

No, if the legal basis for the initial MA was under 'well established use' the Paediatric Regulation is not triggered, and therefore there is no requirement for a PIP.

Can you elaborate on cases like Glivec/Tasigna vs Imatinib Teva? Any risk of "monopoly" for an orphan disease when the same applicant gives consent to itself?

The orphan regulation allows for similar medicinal products breaking the market exclusivity of orphan products in case they can fulfil any of the derogation stipulated in the legislation. Experience shows that the derogation in Art 8.3 (a) which allows the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant has only been used very rarely in the 21 years of the history of the regulation and as such is a very limited risk.

Given that severe COVID-19 pneumonia could potentially cause pulmonary fibrosis, could the EMA consider prioritizing these diseases and possible drugs for them?

EMA's role is to evaluate new medicines to recommend whether they can be marketed in the EU, and to monitor their safety once on the EU market. EMA has mechanisms to prioritise any medicine where there is unmet medical need (scientific advice, PRIME, accelerated assessment), but it has no role in advising what type of medicines companies should develop.

EMA assesses highly needed medicines as a matter of priority pandemic or not. It uses specific regulatory tools such as accelerated assessment procedures aimed at fast tracking the assessment of medicines that are most needed. PRIME is also used to enhance interaction and early dialogue with developers of promising medicines. Development plans are then optimised, and evaluation sped up to ensure that much needed medicines can reach patients earlier.

How can big pharma, who have bought licences from SMEs, be held accountable to not prematurely terminate promising clinical trial (redefining their pipelines)?
The development of a candidate medicinal product is the remit of the developer, the Agency's role in the pre-marketing phase is to stimulate and guide with the aim of getting a safe and effective product to the market. However, it is the developer who will decide whether to continue a development or not.

What is the percentage of repurposed drugs in the total number of approved orphan drugs in Europe?

EMA does not systematically collect these statistics. One publication estimates that about 1 in 5 orphan drugs are repurposed.

Will participants receive a confirmation of attendance for continuing education credits?

No, we cannot issue a certificate to confirm your attendance.

PRIME

What are common mistakes made by applicants for PRIME?

A common limitation of applications not accepted in PRIME is the robustness of the evidence that would support that a product has the potential to significantly address an unmet need. The existence of unmet need in the condition is not per-se sufficient to grant PRIME designation: the available data on the product should be presented in a clear manner to support mechanistic and (if available) clinical rationale to address that need.

What are the reasons for not accepting a medicinal product for the PRIME Programme?

There are mainly two reasons for not accepting a medicinal product. Either that an unmet need in the sought indication is not justified, or that the available evidence does not support that the product could significantly address the unmet need.

Why are so many PRIME applications failing? It seems a large number of PRIME applications are not accepted - what is the explanation for this?

The PRIME scheme is aiming at products that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. Compelling evidence to support this assumption is expected, or (for SME early entry), a clear mechanistic/pharmacodynamic rationale. Additionally, if a product is in a late clinical stage, only limited support to development can be provided, and this may be a reason for rejection.

Is there still a merit to apply for the PRIME when the drug development is already at Phase III or can this be a reason to reject an application?

The benefits from inclusion into the PRIME scheme factor in the discussion on eligibility. Given that one of the key aims of the scheme is to provide scientific advice at key development milestones, late-stage of development close to filing of an MAA, or when the design of the Phase III trials is already finalised, is not in line with the aims of the scheme.

When a product has been accepted for PRIME, can the regular timelines as defined by EMA for the next steps like kick-off meeting be extended by the Applicant?

The Kick-off meeting timing is established in a post-designation teleconference with the Applicant, taking into account the best timing to provide input in development/advice plans.

Is PRIME an option if a company in already conducting pivotal studies and has had EMA scientific advice?

As also discussed above, the benefits from inclusion into the PRIME scheme factor into the discussion on eligibility, as the scope is to provide support to development leading to an MAA. If the pivotal studies are ongoing, the opportunity for this support is very limited and not in line with the aims of the scheme.

What is the main difference between PRIME and Accelerated assessment?

Accelerated assessment is a procedural pathway that provides for shorter timetables for assessment of a marketing authorisation application, for products expected to be of major public health interest, particularly from the point of view of therapeutic innovation . PRIME is a support scheme to provide guidance to accelerate development. PRIME products qualify for an accelerated assessment of the marketing authorisation application. Products can qualify for Accelerated assessment even if they are not PRIME designated.

Can PRIME be compared to Priority Medicines Review at FDA, with rolling reviews?

The PRIME scheme allows the Rapporteur and their team to follow the advancements of the development of a product and advise along the way. While the EU regulatory framework does not explicitly provide for the possibility of "rolling review" for products in PRIME, product is followed across its development thanks to the early appointment of the Rapporteur.

What can an applicant do to increase the chances to be accepted to PRIME?

The applicants may focus on the robustness of evidence, and the contextualisation of the observations versus the already used standard of care in the sought indication. If a subpopulation or subset of symptoms is targeted, biological plausibility and clinical capability to identify such subsets should be discussed too.

ACADEMIA

Is there any plan to provide a cookbook for inexperienced experts to follow while preparing and submitting files to EMA?

Several resources already exist and may provide guidance to the inexperienced stakeholders.

For academic sector, please refer to this visual step-by-step guide on how to submit the files: https://www.ema.europa.eu/en/documents/leaflet/ema-tools-available-medicines-developers-academic-sector_en.pdf

In addition, the SME user guide can also be helpful for academia. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/user-guide-micro-small-medium-sized-enterprises_en.pdf

How can Academia from non-EU (e.g. Switzerland) interact with EMA, e.g. receive PA, PRIME, or submit ODD to EMA?

The European Commission, European Medicines Agency (EMA), Swiss Federal Department of Home Affairs (FDHA) and the Swiss Agency for Therapeutic Products (Swissmedic) have had confidentiality arrangements in place since 2015, allowing for the exchange of confidential information as part of their regulatory and scientific processes. The European Union (EU) and Switzerland also have a mutual recognition agreement (MRA) in place on good manufacturing practice (GMP) compliance. ODD is included in the confidentiality agreement. For agreement with other non-EU countries please see https://www.ema.europa.eu/en/partners-networks/international-activities/bilateral-interactions-non-eu-regulators

How is the EMA promoting regulatory support to academia?

EMA engages with stakeholders at events and conference and includes presentations on EMA support to innovation, SMEs and academia. Academia liaison also proactively interacts with academia via dedicated meetings, learned societies and umbrella organisations to increase visibility of regulatory support from the Agency.

SME

Does a SME have to pay for assistance from the EMA SME office?

Assistance from the SME office is offered to companies registered as SMEs with EMA and it is free of charge (see, how to apply for SME status)

For SMEs, what are the rules when the product is co-developed by e.g. 2 SMEs which both individually fit with the criteria, but no longer when taken together?

For SME status, ownership in terms of capital or voting rights between entities in a group are considered for SME criteria compliance. The SME office can be contacted to discuss specific cases: SME@ema.europa.eu

Are the incentives for SME also available to Academia?

SME incentives are specific to SMEs registered with EMA.

There are specific incentives for academia such as assistance provided by the academia office and fee incentives for protocol assistance (Link).

A company with HQ in Europe but affiliates in the Rest of the World (RoW) need to have 250 employees in total (Europe + RoW) to be designated SME?

A mother company and affiliates are considered as being a group and therefore the total headcount will be taken into account. This is explained in the user guide to the SME definition (Link). The SME office can be contacted to discuss specific cases: SME@ema.europa.eu

How are fees calculated if you lose your SME status during the MAA assessment period?

The SME office can be contacted to discuss specific cases (i.e. merger, acquisition, out-licensing): SME@ema.europa.eu

For SME thresholds, can an EU based entity qualify if either < 50 M euro turnover OR balance sheet of < 43 M euro, OR both are needed?

The company needs to have an annual turnover of not more than 50 million euros OR a balance sheet total of not more than 43 million euros. This is in addition to compliance with the staff/headcount of less than 250.

For a Rest of the World (RoW) SME what are the expectations concerning company registration in the EU?

The company must have a subsidiary established in the EU that will apply for SME status or must register as an SME through a regulatory consultancy company that is based in the EU and has an active SME status.

Who can I talk to at EMA to understand which scheme best applies to my product (PRIME, SA, ITF etc)?

If you are an SME, you can contact the SME office SME@ema.europa.eu

If you are an academia, you can contact the academia office academia@ema.europa.eu

If a company receives SME status but then grows fast (>250 employees), will the company then loose it SME status?

If an enterprise exceeds the headcount or financial ceilings during the course of the reference year, it will retain its SME status with which it began the accounting year. However, it will lose its SME status if it goes above the ceilings for 2 consecutive accounting periods. This is explained in the user guide to the SME definition (Link).

IRDiRC ODDG:

How do we access The IRDiRC Orphan Drug Development Guidebook?

Please find the relevant information on the IRDiRC website:
Information on the Taskforce - https://irdirc.org/activities/task-forces/orphan-drug-development-guidebook-task-force/
Information on the materials developed - https://irdirc.org/orphan-drug-development-guidebook-materials/
The publication in Nature Review Drug Discovery: https://www.nature.com/articles/d41573-020-00060-w
The video tutorial: https://www.youtube.com/watch?v=QMJW85VP3Y8&feature=youtu.be
The interactive website: https://orphandrugguide.org/

How will this ODDG interact with the SME office/ITF?

The ODDG is not meant to replace the interactions of the developers with the EMA SME office/ITF, but rather to help pointing towards these resources and/or to be used as a complementary supportive tool. ITF and SME office are some of the Building Blocks listed in the ODDG:
https://orphandrugguide.org/bb/ODDG_TF_Building%20Block%20Form_E101.pdf
https://orphandrugguide.org/bb/ODDG_TF_Building%20Block%20Form_E115.pdf

Both Building Blocks are presented in the Gannt-like graphical representations of the development cases, e.g.:
https://orphandrugguide.org/developmentcase/TRADITIONAL-TECHNOLOGY-TARGETING-A-SUFFICIENTLY-WELL-UNDERSTOOD-RARE-DISEASE

Does the guidebook also cover Intellectual property rights, patent protection, supplementary protection certificates etc.?

These topics were not included as such in the Guidebook - the focus was mainly on initiatives, tools, resources that have been specifically designed, or present a particular interest, for the Rare Disease therapeutic development.

Will there be incentives for Medical Devices development for Rare diseases in the future?

For the moment we were not able to explore broadly the Building blocks that may be related to Medical Devices. IRDiRC ODDG only included a few building blocks from US and Japan jurisdictions, e.g. Humanitarian Device -
https://orphandrugguide.org/bb/ODDG_TF_Building%20Block%20Form_U202.pdf

Further literature on orphan criteria in the EU:

1. Defining orphan conditions in the context of the European orphan regulation: challenges and evolution. O'Connor et al, Nat Rev Drug Discov. 2018 Sep 12.
2. Use of biomarkers in the context of orphan medicines designation in the European Union. Tsigkos et al. Orphanet J Rare Dis. 2014 Jan 27;9:13.
3. Non-clinical data supporting orphan medicinal product designations in the area of rare infectious diseases Shean M et al, Drug Discov Today. 2019
4. Nonclinical data supporting orphan medicinal product designations: lessons from rare neurological conditions. Sheean M et al, Drug Discov Today. 2018 Jan;23(1):26-48.
5. Establishing medical plausibility in the context of orphan medicines designation in the European Union. Tsigkos S, et al. Orphanet J Rare Dis. 2014 Dec 5;9:175.

6. Animal models for metabolic, neuromuscular and ophthalmological rare diseases. Vaquer G. et al, Nat Rev Drug Discov. 2013 Apr;12(4):287-305.
7. Establishing rarity in the context of orphan medicinal product designation in the European Union. Tsigkos S et al. Drug Discov. Today 2018. Mar;23(3):681-686.
8. Evolving prevalence of haematological malignancies in orphan designation procedures in the European Union. Polsinelli B, et al, Orphanet J Rare Dis. 2017 Jan 21;12(1):17.
9. Marketing authorisation of orphan medicines in Europe from 2000 to 2013. Hofer et al. Drug Discovery Today 2018 23(2) 424-433.
10. Demonstrating Significant Benefit of Orphan Medicines: Analysis of 15 years of Experience in Europe. Fregonese L et al. Drug Discovery Today 2018, 23 (1), 90-100.
11. European regulation on orphan medicinal products: 10 years of experience and future perspectives. The Committee for Orphan Medicinal Products and the European Medicines Agency Scientific Secretariat. Nature reviews Drug Discovery 2011 10: 341.