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National Forum on
Rare Diseases and Pediatric Indications

With the nonconditional contribution of Farmindustria

Statement on the review of the European Commission of the two EU Regulations on orphan and pediatric indications.

April 2023

The document was written before 04/26/2023, the date on which the European Commission submitted its proposal for the revision of the pharmaceutical legislation. (Reform of the EU pharmaceutical legislation Available at: https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en Accessed April 26, 2023)

Therefore, it makes no explicit reference to this proposal but is based on what is publicly available at the time of its writing.

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Background[i]

Regulation (EC) No. 141/2000 of the European Parliament and of the Council of December 16, 1999, on *orphan medicinal products* (OMPs) has contributed to important advances in the field of *rare diseases* (RDs) and the development of new medicines. Due to scientific research endeavors, such as the completion of genomic sequencing in the late 1990s, there has been an increase in research activity that has made new therapies available to patients. The incentives provided by Regulation (EC) No. 141/2000 have certainly supported scientific progress. Similarly, the promising pipeline of drugs under development could bring real value to those patients for whom no treatment options currently exist.

The same intent applies to Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of December 12, 2006, on medicinal products for pediatric use, which was enacted to improve the health of children in Europe through incentives, regulatory measures, and clinical research support by facilitating the development and availability of medicines for individuals aged 0–17 years.

Since their adoption, these two regulations have led to an increase in drugs for RDs and children in many therapeutic areas. Despite great successes, however, it is essential to acknowledge that there are ongoing *unmet medical needs* (UMN) that must be addressed. UMN was among the main objectives of the two regulations and remains relevant today.

- **EU-wide availability of and access to orphan drugs**
    - There continue to be substantial differences between *Member States* (MS): while in some countries, patients have access to most OMPs, in others such access is not guaranteed. Differences also exist in the speed with which drugs become available. The problem can be addressed by an EU regulation only to a very limited extent, as the differences stem in large part from national policies and decision-making processes. Indeed, with the development of more and more OMPs, as defined by Regulation (EC) No. 141/2000, there is a real risk of increasing inequality in access to care among RDs patients. Indeed, increasing pressures related to the sustainability of national health care systems could force more countries to adopt restrictive reimbursement policies. Regulation (EC) No. 141/2000 contains neither the tools nor the mandate to intervene at this level. Therefore, achieving this goal would require further action from individual MS (Study to support

the evaluation of the EU Orphan Regulation Final report, 2019).

- **Impact of scientific and industry developments**
    - These mostly have a clear positive effect on the potential for developing new treatments for RDs patients by bringing together knowledge and resources and making better use of available data. At the same time, the framework and implementation of Regulation (EC) No. 141/2000 may not fully meet the requirements that arise from scientific advances. Therefore, it is important that the framework be sufficiently up to date to take advantage of opportunities, such as the use of biomarkers to define a medical condition or a valid subset for orphan designation (OD), particularly for rare cancers, or the implementation of new clinical study designs (Study to support the evaluation of the EU Orphan Regulation Final report, 2019).
- **Effectiveness of incentives**

    All incentives help support the development of new therapies for RDs and pediatric indications. The effectiveness of incentives varies depending on factors such as developer experience, therapeutic area, and product characteristics (e.g., the need to demonstrate significant benefit), the stage of product development, or other (e.g., the existence of other intellectual property or regulatory protections). However, the effects of individual incentives cannot be isolated from one another, nor can the effectiveness of the incentives offered by Regulation (EC) No. 141/2000 be seen as separate from that of incentives offered by similar regulations in other jurisdictions, such as the United States. Are incentives such as *market exclusivity* (ME), in its current form, still able to stimulate development in areas of high therapeutic need for patients? Or should they be coupled with more gradual modulations that can better target research to areas that are still neglected or to the actual availability of the drug to the patients? Similarly, the identification of UMN as a parameter for directing clinical research and establishing links to the incentive system has not always proven capable of capturing patients' priority interest in drugs of added therapeutic value. The incentive system should be able to both attract investment to provide real answers for patients and make drugs available for all MS, balanced fairly between companies' obligations and facilitation by the European Commission (EC) (Study to support the evaluation of the EU Orphan Regulation Final report, 2019).
- **Effectiveness in addressing unmet needs.**

- In terms of the availability of OMPs and the speed with which they become accessible, there are substantial differences among MS. These differences are such that in some MS, patients can hardly appreciate the impact of the regulation. Although authorized products cover a wide range of therapeutic areas and indications, some clustering is apparent, particularly around cancer treatments. This has been associated with a number of factors,including the availability of guidelines, alignment with the existing research and development pipeline, and the availability of other treatment options (Study to support the evaluation of the EU Orphan Regulation Final report, 2019). From an access perspective, it is possible to grant *conditional marketing authorization* (CMA) to drugs that are promising from a clinical benefit perspective in areas considered to be in high therapeutic need, with evidence required to confirm the efficacy of treatments and understand their real value to patients (Study to support the evaluation of the EU Orphan Regulation Final report, 2019). Currently, out of 146 OMPs approved by the European Medicines Agency (EMA), 26 are approved with a CMA, 20 with exceptional circumstances,[1] and 18 with *accelerated assessment* (AA) (Download medicine data, EMA output generated May 24, 2023).

- **Impact on OMP for pediatric use**

Since the inception of Regulation (EC) No. 141/2000, 111 out of 142 medicines (78%, of which 68% have adult and pediatric indications and 8% are pediatric only) have been placed on the market for orphan conditions that alsoaffect children (Study to support the evaluation of the EU Orphan Regulation Final report, 2019). This includes 14 drugs for exclusively pediatric conditions, while most cover conditions that affect both adults and children. In addition, again according to the Study to support the evaluation of the EU Orphan Regulation Final report, as of 2019, there are 56 OMPs approved for use in children, or about 50% of the total. This result is likely due to the fact that Regulation (EC) No. 141/2000 and Regulation (EC) No.1901/2006 do not provide tools or incentives to specifically target development for conditions affecting children (Study to support the evaluation of the EU Orphan Regulation Final report, 2019). Since about 50% of all MR

[1] The EMA may also grant AIC in the absence of complete data in exceptional circumstances. Unlike conditional AIC, in which AIC is granted with the expectation that the sponsor will provide such data within an agreed time period, the EMA may grant authorization in exceptional circumstances when complete data cannot be obtained even after authorization. This route to authorization normally does not lead to a standard AIC.

occur in childhood (EURORDIS - Rare Diseases Europe, 2005), there is a clear need to develop OMPs for pediatric indications. Therefore, there should be an explicit link between the two EU regulations in the form of an extension of the period of ME for OMPs for which trials have been completed in the pediatric area.

- **Competitiveness of the pharmaceutical industry in Europe**
    - Regulation (EC) No. 141/2000 has improved the framework for research and development of medicines for RDs. This has led to an increase in the number of actors involved in academia and industry, creating research networks and greater collaboration between pharma companies, academia, and patients. However, the Regulation does not oblige companies to conduct research and development in the EU, and the decision regarding where to conduct these activities depends on other factors. Furthermore, the Regulation does not provide tools to guide research and thus can only indirectly contribute to the competitiveness of the pharmaceutical industry in Europe (Study to support the evaluation of the EU Orphan Regulation Final report, 2019).
- **Costs and benefits**
    - In the context of Regulation (EC) No. 141/2000, it is possible to identify various types of costs and benefits that impact stakeholders in different ways and contribute to the overall efficiency level of the health care system. On the one hand, there are the additional costs associated with spending on OMPs resulting from Regulation (EC) No. 141/2000 and the health care costs associated with treatment with OMPs. On the other hand, these costs should be matched by savings related to treatment alternatives and improved quality of life for patients. It is not possible to establish the overall effect of Regulation (EC) No. 141/2000 because information on OMPs is not always available. In addition, the broader economic benefits are difficult to establish, primarily because of the large difference between the diseases involved. However, the balance is likely to be a positive value since RDs are often highly disabling and represent a heavy burden on everyone. The exact distribution of health care costs between public entities and patients is unclear. Although these estimates of costs and benefits to different stakeholders are informative, they cannot directly answer the question of whether this balance of costs and benefits is proportional or "fair." It is essentially a subjective assessment based on the value placed on health benefits and what is considered a reasonable return on investment (Study to support the evaluation of the EU Orphan Regulation Final report, 2019).

- **Administrative burden**
    - Developers of (potential) OMPs are not required to apply for OD or take advantage of incentives offered under Regulation (EC) No. 141/2000. Sponsors of drugs with OD must comply with the requirements established under Regulation (EC) No. 141/2000 (e.g., submit annual reports) and have the option to withdraw their OD at any time. The orphan designation also places an administrative burden on the EMA, a commitment that is bound to increase as the number of applications continues to grow. The increased workload also affects members of the Committee for Orphan Medicinal Products (COMP). The administrative burden associated with their work falls largely on the institutions from which they come, which nevertheless receive no input. All this puts a strain on the system and could affect its long-term sustainability.
- **Consistency and complementarity with other EU regulations and national interventions**
    - The overall regulatory system for pharmaceuticals in the EU is quite complex and could benefit from a more holistic and streamlined architecture. This complexity is apparent, for example, in the use of seemingly similar but distinct concepts (e.g., "significant benefit" versus "greater public health interest" or "added value") between regulations or procedures and in the way different evaluation processes are organized in relation to each other. There are strong links between the EMA, national health authorities, and *Health Technology Assessment* (HTA) agencies. These agencies are aligned in their goals to provide RDs patients with the care they need, recognizing the role played by the pharmaceutical industry. However, there appears to be a lack of consistency between different national policies in terms of pricing and reimbursement of OMPs, resulting in different levels of access across the *European Economic Area* (EEA).

At the central level (EMA) there is an absolute risk assessment that does not take into account a comparative analysis of the risk–benefit ratio between medicinals with the same therapeutic indication. The COMP's assessment of "significant benefit" can also be accomplished through indirect comparison. These assessments, however, do not follow a pre-specified methodology, and it is not certain that this approach aligns with the comparative assessment methodologies employed by HTA bodies at the national level. In fact, within MS, a key point in the entire pricing and reimbursement process and the actual availability of OMPs concerns the definition of degrees of benefit among existing products conducted through *relative effectiveness assessment* (REA). The extent of the assessment can also differ very often, if the medicinal at the central regulatory level (EMA) is authorized with an AA with/without CMA/EC, it will be more complex to authorize it at the local (HTA/ payer) level due to data being unavailable or nonexistent.

- **Patients' expectations regarding the concepts of OD and AIC**
    - Only a small proportion of orphan designations make it to the end of the approval process. This can increase the expectations of patients with diseases for which drugs have been granted orphan designation but that may not have successfully completed the various stages of development. This is no different from other areas of development. There is also some inherent divergence in the process between the application of the Orphan and Therapeutic Indication concepts (see Box 1 on page 36) (Regulation [EC] No. 141/2000 of the European Parliament and of the Council of December 16, 1999 on orphan medicinal products, 1999).

Therefore, the EC has seen fit to initiate a review (Inception Impact Assessment Revision of the EU legislation on medicines for children and rare diseases, 2020) of the regulatory framework for orphan and pediatric medicines in the EU. This is part of the broader review of EU pharmaceutical legislation initiated under the European Pharmaceutical Strategy adopted by the EC in 2020 to create a regulatory framework fit for the future and support the industry in promoting research and technologies to meet patients' therapeutic needs.

Both Regulation (EC) No. 141/2000 and Regulation (EC) No. 1901/2006 were designed to address specific UMN related to specific populations, although the tools they use differ substantially:

- Regulation (EC) No. 141/2000 aims to encourage research, development, and authorization of new drugs for MR by providing specific incentives that balance the risk associated with a field in which the small size of the population to be treated often implies a lack of adequate knowledge.
- Regulation (EC) No. 1901/2006 mainly provides for *obligations* in two ways: 1) it obliges companies that already develop products for adults to conduct additional clinical studies for possible use in children and 2) it provides incentives for companies that fulfill this obligation through the implementation of a pediatric investigation plan (PIP) to compensate for the additional costs.

In light of the new regulatory and institutional scenarios, upcoming changes in the regulatory framework will be crucial to ensure adequate incentives for innovation developers (pharma industries or small and medium-sized enterprises [SMEs]). Such revision, however, must be directed toward addressing health needs, which to date have not been fully met, with solutions that are of value to individuals and the community and that prove contextually sustainable.

Role of the Forum and structure of the document

The shared goal of the National Forum on Rare Diseases and Pediatric Indications (FMRP) is to ensure a high level of health protection for all by encouraging innovation and clinical research; the intent, therefore, is to create a collaborative space that can bring together different perspectives (scientific, institutional, patient/citizen associations, and the pharmaceutical industry) with two main goals:

1. To provide a reading of the experience of the last 20 years of European regulations on RD treatments and pediatric indications.
2. To share with institutions possible elements of regulatory improvement also in view of the review of pharmaceutical legislation (Inception Impact Assessment Revision of the EU legislation on medicines for children and rare diseases, 2020; Public consultation factual summary report Impact Assessment - Study supporting the Impact Assessment of the revision of the EU legislation on medicines for children and rare diseases: Consultation outcome, 2021)

The value of this initiative is in facilitating the sharing of elements and actions, both in terms of analysis and proposals. This process, rooted in the needs of patients while respecting different legitimate interests, can establish a common foundation from which to pursue priorities. Each expert was invited to participate based on their experience, expertise, context, and perspective.

The operational modalities of the Forum

The FMRP was established with the nonconditional contribution of Farmindustria and coordinated by the Alta Scuola di Economia e Management dei Sistemi Sanitari (ALTEMS), guaranteeing the scientific nature of the approach, the tertiary nature of the discussion, and the confidentiality of all participants.

The discussions took place behind closed doors according to *Chatham House Rules,* which stipulate that Forum participants are free to use the information they receive as long as they do not reveal either the identity or affiliation of the speaker(s) or any other participant. In this way, members have freely expressed personal opinions based on their own experiences and perspectives but not representing the institutions to which they belong.

The working method and steps

The FMRP acted according to a program based on five key moments:

- Initial phase (*scoping meeting*) on November 14, 2022: The first meeting between all stakeholders, during which rules of engagement and priorities for discussion were shared and the agenda for activities was set.
- Deepening phase (December 15, 2022, and January 30, 2023): The richness of the content of the two regulations and the complexity of the areas of discussion led the working group to focus oncertain aspects considered key in the process of revising the European regulatory framework inherent to MR and pediatric medicines.

  For this reason, the discussion focused on the following eight areas of focus:

  - Access times (including early access)
  - Investments
  - Early (and continuous) access
  - Unmet Medical Need
  - How to define rarity
  - Pediatric regulation
  - Harmonization of European regulations

- Document formalization phase: The suggestions that emerged, in the presence of unanimous agreement, were synthesized by ALTEMS researchers, identifying for each point the *context* and the shared *proposal*. The final document does not contrast with those prepared and already submitted by the institutions/associations involved in this exercise. Within this document, where joint positions were derived from positions previously expressed by individual contributors, they have been included as *references*.
- Closing phase and sharing with Forum members: The document was shared with all Forum members for appropriate review.
- Dissemination phase: The shared document will be presented through a *workshop* in Rome on May 9, 2023.[2]

[2] The document was written before 4/26/2023, the date on which the EC submitted its proposal for the revision of the pharmaceutical legislation (Reform of the EU pharmaceutical legislation. Available at: https://health.ec.europa.eu/medicinal- products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en. Accessed April 26, 2023). Therefore, it does not make explicit reference to that proposal but is based on what was publicly available at the time of its drafting.

Access Times (1)

Background

In Italy, during the four-year period 2018–2021, the average time from European Market Access (MA) to drug access was 477 days (IQVIA, 2022). As of December 31, 2021, out of the total 130 OMPs authorized by the EMA, 122 were available in Italy. Of the remaining eight drugs, four have been marketed as of 2022, two are in the process of pricing and reimbursement, and two have not been the subject of an application for price and reimbursement (P&R) negotiation by the manufacturing companies (OsMed, 2021).

Among the elements presented by the EC referring to access to medicines, which were the subject of public consultation (Inception Impact Assessment Revision of the EU legislation on medicines for children and rare diseases, 2020), were:

- Increasing the availability of therapeutic alternatives, for example by allowing a generic or biosimilar product to enter the market more quickly.
- Allowing pharmaceutical companies that no longer wish to focus their resources on developing drugs for a rare disease or pediatric condition to transfer their patent and technologies to another company, encouraging further development. Companies that lose commercial interest in a product should be encouraged to transfer it to another company rather than withdraw it, thus ensuring continuity in development.
- Tying the eligibility for incentives/rewards to the timely launch of OMPs by the companies developing them in all MS once a Europe-wide MA has been obtained.

For completeness of information regarding access, it should be noted that Italy has provided some important tools that facilitate *early access*, in some specific situations, to medicinals not yet available in the national territory for the treatment of RDs (Law No. 648/1996, 1996; Ministry of Health Law No. 326/2003, published in OJ No. 274, Nov. 25, 2003 - Ordinary SupplementNo. 181, 2003). However, these measures were not always initiated to address specific needs related to RDs. They often deviate from the ordinary path of negotiation, in some cases interfering with certain aspects of negotiations in terms of expectations, timing, and access methods.

Proposal

The FMRP recognizes the limitations of addressing access as directly related to pharmaceutical *governance* and public health strategies/policies/regulations of individual MS and only indirectly to the implementation of the two EU regulations (Regulation [EC] No. 141/2000 of the European Parliament and of the Council of December 16, 1999 on orphan medicinal products, 1999; Regulation [EC] No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for pediatric use, 2006).

The revision of the two regulations should have a positive impact on patients' right to access a high level of human health protection by making medicines available and more affordable in all MS. Health disparities should be reduced, as the goal is to offer the same quality of treatment to all patients in the EU, ensuring that children and RD's patients are treated like any other patient.

Ordinary access should also be distinguished from *early access*. Early access is the responsibility of individual MS (for Italy: Law No. 648/1996, 1996; Ministry of Health Law No.326/2003 published in OJ No. 274, Nov. 25, 2003 - Ordinary Supplement No. 181, 2003), while ordinary access (approval and *postmarketing*) is linked to possible EMA regulatory *commitments*, such as *specific obligations* for CMAs[3] or those related to pharmacovigilance activities such as *post-approval effectiveness*[4] or *safety*[5] *studies* (post-approval effectiveness studies [PAESs] or post-approval safety studies [PASSs]).

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[3] The EMA supports the development of medicines that address UMN. In the interest of public health, applicants may be granted CMA for such medicines based on less complete clinical data than normally required when the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still needed. Medicines for human use are eligible if they are intended for the treatment, prevention, or diagnosis of seriously debilitating or life-threatening diseases. This includes ODs. It is also intended for use in a public health emergency, such as a pandemic. Less complete non-clinical data may also be accepted for these medicines. The legal basis is Article 14a of Regulation (EC) No. 726/2004. The provisions for granting CMA are further elaborated in Regulation (EC) No. 507/2006.

[4] A PAES, as provided for in Commission Delegated Regulation (EU) No. 357/2014, is defined as an efficacy study required by a Competent Authority under at least one of the situations provided for in that regulation. Data resulting from such a PAES conducted in the context of an authorized therapeutic indication must be submitted, as it is considered important to supplement available efficacy data when there are reasonable scientific uncertainties about aspects of the evidence of future benefits that can only be addressed after authorization. The results of the PAES can affect the risk–benefit ratio of the drug or product information. Such a PAES may be mandated: 1) at the time the MA is granted if doubts are identified regarding some aspect of the drug's efficacy that can be resolved only after the drug is marketed or 2) after a MA is granted if the understanding of the disease or clinical methodology or use of the drug under real-life conditions indicates that previous efficacy evaluations may need to be significantly revised. A PAES may also be required in the specific situations of a CMA, a MA granted in exceptional circumstances, a MA granted to an advanced therapy medicinal product, pediatric use of a medicinal product, or a referral procedure initiated under Article 31 or Article 107i of Directive 2001/83/EC or Article 20 of Regulation (EC) No. 726/2004. However, these are outside the scope of the delegated regulation.

[5] A PASS is a study conducted after a drug has been authorized to obtain additional information about its safety or to measure the effectiveness of risk-management measures. The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for evaluating the protocols of PASSs and assessing their results. The purpose of the information in PASSs is to assess the safety and risk–benefit profile of a drug and support regulatory decision-making. They aim to identify, characterize, or quantify a safety hazard; confirm the safety profile of a drug; or measure the effectiveness of risk-management measures. PASSs can be clinical studies or non-interventional studies. PASSs are either imposed or voluntary. AIC holders (MAHs) are required to perform imposed PASSs. These include studies that are a specific obligation for an AIC granted in exceptional circumstances and other studies that the PRAC requires the company to perform. Voluntary PASSs are sponsored or conducted by MAHs on their own initiative. They also include non-mandated studies required in risk-management plans (RMPs).

Also, please note that not all OMPs have a CMA; therefore, these drugs follow the same authorization routes (normal route) with or without AA.[6]

At the European level, it would be important to provide for an Immediate Access Fund to:

- support the generation of additional evidence from actual clinical practice, based on *real-world data* (RWD) planned during the early stages of drug development and discussed during the *scientific advice* phase with EMA and/or European Network of HTA (EUnetHTA) to manage clinical uncertainty.
- measure the added value of OMPs or treatments for MR and those for pediatric conditions.

With this in mind, the FMRP agrees on the importance of the HTA process and the new EU regulation for HTA.

At the national level, on the other hand, early access mechanisms have structural problems in terms of the sometimes subjective and discretionary interpretations of regulations (definitions of requirements), economic subsistence of dedicated funds (see the case of the National AIFA Fund 5%) (Ministry of Health Law No. 326/2003 published in OJ No. 274, Nov. 25, 2003 - Ordinary Supplement No. 181, 2003), and, most importantly, the recent requests for changes in the drugs included in Law 648/1996 resulting from the implementation of the AIFA Guidelines on Demand for Reimbursement and Pricing (Ministry of Health Decree Criteria and methods by which the Italian Drug Agency determines, through negotiation, the prices of drugs reimbursed by the National Health Service) (20A03810; OJ General Series No.185 of 24-07-2020, 2019).

It is crucial to strengthen, harmonize, and, most importantly, enforce the transparency of these instruments to ensure rapid access to drugs deemed worthy, especially at the local (regional) level of the country.

[6] Expedited assessment reduces the time for the EMA Committee for Human Medicinal Products (CHMP) to review an AIC application. Applications may be eligible for expedited evaluation if the CHMP decides that the drug is of high interest for public health and therapeutic innovation. The evaluation of an AIC application under the centralized procedure can take up to 210 days, not counting downtime when applicants must provide additional information. Upon request, the CHMP can reduce the period to 150 days if the applicant provides sufficient justification for an expedited evaluation.

Investments (2)

Background

Regulation (EC) No. 141/2000 establishes a two-step process: the orphan designation of new molecular entity during the drug development phase and the subsequent granting of ME once the OMP has been authorized. This allows developers to both access funding for RD research and development provided at the European or national level and to more easily attract support from private investors. It is only after the long and complex process of developing an OD has been completed that the company can apply for *marketing authorization* (MA) at the EU level.

An authorized OMP will enjoy a 10-year period of ME, during which similar drugs for the same indication cannot be marketed. This may be extended for an additional two years if a PIP[7] is completed, outlining the relevant data from the development of the drug to support authorization for administration in children.

Based on the definitions in Article 3 of Regulation (EC) No. 847/2000, the assessment of similarity between two medicinal products under Article 8 of Regulation (EC) No. 141/2000 takes into consideration the main molecular structural features, mechanism of action, and therapeutic indication. If there are significant differences in one or more of these criteria, the two products will not be considered similar. Article 8(1) of the Regulation provides the relevant criteria for assessing similarity between two OMPs. In particular, Article 8(3) of Regulation (EC) No. 141/2000[8] describes three types of exceptions to ME provided for in Article 8(1) of that Regulation: a) the original OMP authorization holder has given consent to the second applicant, b) the original OMP authorization holder is unable to supply a sufficient quantity of the medicinal product in question, or c) the second applicant demonstrates in its application that the second medicinal product, although similar to the already authorized OMP, is safer, more effective, and otherwise clinically superior.

The reference articles of Regulation (EC) No. 141/2000:

[7] A PIP is a development plan designed to ensure that the necessary data are obtained through studies in children to support the authorization of a medicine for children. All MA applications for new medicines must include the results of studies described in an agreed PIP unless the medicine is exempt due to deferral or waiver. This requirement also applies when an MA holder wishes to add a new indication, pharmaceutical form, or route of administration for an already authorized medicine covered by intellectual property rights.

8 EC Communication C(2008) 4077. Available at http://eur- lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:242:0012:0016:EN:PDF Accessed April 1, 2023

- Article 8: ME, which gives the MAH a temporary exclusive right (in addition to the normal *data protection* provided for newly authorized medicines).
- Article 6: Protocol assistance, which offers the sponsor of a drug with OD the opportunity to seek advice from EMA on conducting tests and trials necessary to demonstrate the quality, safety, and efficacy of the drug.
- Article 7 sub-2[9]*: Fee* waivers, which offer full or partial fee waivers for MA applications of medicines designated as ODs (especially for SMEs).
- Article 9: Aid for research, allowing for other incentives to stimulate the development and commercialization of OMPs, either at the community or individual MS level.

Regulation (EC) No. 141/2000 is credited with strengthening research and development of RDTs, leading to an increase in the number of players in the field in both academia and industry. Research networks have been established, public–private collaboration between academia and companies has been enhanced, and thanks in part to patient involvement, the *pipeline* of OMPs in development has grown. The climate has improved overall. However, the regulation does not contain any provisions that, despite the incentives offered, would constrain the conduct of research and development (R&D) activities in the EU. To date, therefore, a pharmaceutical company's decision-making process on where to conduct R&D depends largely on other factors, such as the ability to conduct clinical trials, the presence of research networks and the availability of researchers, and economic incentives for R&D activities.

Proposal

The Forum does not believe that changing the duration of ME will result in more approvals of OMPs and drugs with pediatric indications; therefore, it agrees to protect **those** already established while potentially employing additional incentives to support the development of drugs to treat ultra-rare conditions.

The Forum also points out that the ME incentive lapses from the moment a new OMP demonstrates superiority over an existing OMP in terms of *significant clinical benefit*. This drives more competition

[9] A special Community contribution, other than that provided for in Article 57 of Regulation (EEC) No. 2309/93, shall be allocated annually to the Agency (EMA). The contribution shall be used exclusively by the Agency to waive, in whole or in part, all fees due under Community legislation adopted pursuant to Regulation (EEC) No. 2309/93. At the end of each year, the Executive Director of the Agency shall submit a detailed report on the use made of this special contribution. The surplus occurring in a given year shall be carried forward and deducted from the special contribution for the following year.

among pharmaceutical companies, thus incentivizing research in a given area.

The Forum strongly encourages EU funding for research and agrees with the initial objectives of the revision of the two regulations outlined in the Inception Impact Assessment Revision of the EU legislation on medicines for children and rare diseases (2020), namely, to promote research and development of medicines for MR and children, especially in areas of unmet need and in better alignment with patient needs.

EURORDIS[10] - Rare Diseases Europe's "Proposal on the revision of the Orphan medicinal Products and Paediatric Regulation"[11] advises introducing an "Orphan Drug Development Plan" to guide the development of new treatments with ongoing expert input. This establishes a "contractual" agreement between the developer and the regulatory authority to guide development through the different stages that fall within the EMA's scope of activities and would also allow for knowledge-building and supporting interactions with HTA and *payer* bodies (EURORDIS - Rare Diseases Europe, 2022). This proposal, which is also supported by the Forum, suggests the possible modulation of ME based on unmet therapeutic need. To most effectively address the UMN of people living with an RD, a tiered system could be introduced to provide different levels of incentives depending on specific factors. This system could, for example, target very rare to ultra-rare conditions or those lacking any existing treatment options as the basis for an incentive. Products identified as particularly innovative could also receive a bonus incentive. Incentives should also be provided for research funding, using existing facilities such as *European Reference Networks* (ERNs). Similarly, processes that encourage faster access to care, such as early dialogue between the sponsor and regulatory bodies, should be rewarded. A "European Fund" that supports the generation of further *real-world evidence* (RWE), both in the compassionate use context and in the years after the approval, would help collect much-needed comparative data, for example through registries, and should therefore be encouraged (EURORDIS - Rare Diseases Europe, 2022).

To accelerate drug discovery and development for RD and complex pediatric diseases, EFPIA has

[10] Available at https://www.eurordis.org/who-we-are/our-vision-mission/ Accessed April 27, 2023.

[11] This proposal is a contribution from EURORDIS - Rare Diseases Europe and its members, offering concrete recommendations for the upcoming revision of the OMP regulation. With 20 years of experience in following the life cycle of ODs through the OMP regulations in the EU and the FDA Drug Act in the United States, it is mainly based on the experiences of people living with MR in Europe. The proposals have been socialized progressively since 2018 through public consultations, evaluations, events, and EC conferences. Contributors to these proposals have included the *Therapeutics Advisory Group*, the *Drug Information, Transparency and Access* (DITA) *Task Force*, the *Council of National Alliances*, and the *Council of European Federations*.

launched the *Rare Disease Moonshot* project[12], which is based on the efforts of seven different European organizations that have agreed to enter into a collaborative relationship to improve the translational research environment, optimize clinical trials and regulatory pathways, and accelerate the pathway to the diagnosis and treatment of RDs.

[12] Available at https://www.rarediseasemoonshot.eu/ Accessed April 27, 2023.

***Significant Benefit*[ii] (3)**

Background

The EMA COMP assesses whether a drug meets the criteria for OD at two different points: first, when an application for orphan designation of a new entity in the early stages of development is submitted; second, with MA of the new drug along with a positive opinion from the EMA Committee for Human Medicinal Products (CHMP) when the applicant applies for continued orphan designation. The demonstration of significant benefit is based on assumptions made at the time of OD and must be confirmed at the time of MA, supported by comparative data with quantifiable standards of care (SoC). This is one of the criteria an OMP must have to qualify for ME.

Proposal

The evaluation currently conducted by the EMA COMP could incorporate technical elements similar to the arrangements adopted by HTA/payer agencies and scientific societies, such as:

- The use of *ranking/score* (see for example that of ESMO–MCBS Scorecards)[13]
- AIFA's recognition of innovation based on three criteria: therapeutic need, added therapeutic value, and robustness of clinical evidence;[14]
- The French[15] Service Médical Rendu methodology, which considers five criteria: (1) severity of the disease and its impact on morbidity and mortality, (2) indication of the drug, (3) therapeutic alternatives, (4) its role in therapy, and (5) any public health considerations, such as disease burden, impact on community health, quality of clinical trials, etc.; and *Amélioration du Service Médical Rendu*, used to determine the degree of actual clinical benefit in five levels of ASMR and determines the price of the drug by *Haute Autorité de Santé*.

Value frameworks can be a valuable tool for increasing transparency and efficiency in decision-making processes, involving all *stakeholders* according to their roles and the rules of engagement. The conception of value is changing in all health care systems, with the focus no longer merely on achieving the best possible clinical outcome but increasingly on a holistic conception of the patient and the system of care as a whole, embracing considerations of management and financial

[13] Available at https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards Accessed April 27, 2023.

[14] Available at https://www.aifa.gov.it/web/guest/farmaci-innovativi Accessed April 27, 2023.

[15] Xoxi et al., 2022

sustainability. Existing *value frameworks* originate predominantly in the United States and therefore reflect its criticality and needs.

The HTA paradigm, which, like modern theories of value measurement, has been widespread in Europe for much longer, promotes economic rationality and cost-effectiveness in the allocation of health care resources that are probably best suited to universal-access health care systems[16]. The improvement of COMP assessments of *significant benefit* (i.e., through benchmarking closely akin to HTA methodology) is critical in defining the value of drugs not only in regulatory *frameworks* primarily focused on P&R but in the national context as well. Again, the Forum agrees that Regulation (EC) No. 141/2000 needs to be harmonized with HTA.

[16] Boscolo et al., 2021

***Early (and Continuous) Dialogue* (4)**

Background

The predictivity of uncertainty is an important factor for all *stakeholders*, especially patients (major players in the development of a technology) and industry (as the main investor). It is generally believed that *early dialogue* can consider known information about the disease and the status of available therapies and provide guidance toward the early formulation of an *evidence generation* program for a new technology. This is especially true with RDs, where data on the natural history of the pathology are lacking, no known comparators are available, randomized controlled clinical trials are difficult to initiate, etc.

RWD/RWE could be relevant in contexts such as RD or pediatric indications as support for classical drug development. This is confirmed by recent EMA analyses, which also highlight the limitations of RWD/RWE presented in regulatory dossiers. This indicates that the suitability of data for an MAA still requires case-by-case analysis. The main issues discussed with respect to RWE relate to methodological weaknesses, including missing data, poor population representativeness, small sample size, lack of an adequate or pre-specified analysis plan, and the risk of different types of *bias* (mainly selection *bias)*[17] [18]

Early and ongoing dialogues with regulatory authorities and relevant stakeholders are key to optimizing the generation of fit-for-purpose RWEs, enabling their wider use in drug development.

In addition to *early dialogue* and referring to the launch phase of a drug in the EU, it is necessary to have a regulated mechanism that assesses the relative effectiveness of new technologies' at the central (EU) level (EUnetHTA JA WP5: Relative Effectiveness Assessment (REA) of Pharmaceuticals, 2011) to help developers focus on specific areas of interest. This helps avoid overcrowding in certain areas, leaving others uncovered, and assists in finding mechanisms to stimulate possible investments in therapeutic areas where there is a real need. One tool that could serve this purpose is the *joint scientific consultation* (JSC) provided for in the new EU HTA Regulation (Regulation [EU] 2021/2282 of the

[17] Bakker et al., 2023

[18] Selection bias (bias) refers to systematic differences between the baseline characteristics of groups being compared in a clinical trial. The unique strength of randomization is that, when successfully completed, prevents selection bias in the assignment of interventions to participants in the study. Available at https://handbook-5-1.cochrane.org/chapter_8/8_4_introduction_to_sources_of_bias_in_clinical_trials.htm Accessed April 27, 2023.

European Parliament and of the Council of December 15, 2021 on health technology assessment and amending Directive 2011/24/EU, 2021), which aims to uniformly find formulas that properly target investments, including to lower industrial risk.

Proposal

The Forum still highlights the importance of harmonizing this point with European initiatives related to HTA and the related regulation on HTA. It proposes the development of guidelines at the European level similar to those formulated by the FDA to also collect and present data on experience, valid for the development of all new and innovative technologies.

The involvement of ERNs is crucial in this regard (European Reference Network: Clinical practice guidelines and clinical decision support tools program, 2023) to facilitate the collection of data and evidence and foster discussion on conditions and MR that require highly specialized care, knowledge, and concentrated resources. ERNs also use interoperability among registries to optimize data communication at the European level, ensuring harmonization of strategies with clear and shared *policies*.

***Unmet Medical Need*[iii] (5)**

Background

The trend of new MAs for OMPs is increasing, exhibiting a fluctuating pattern (Study to support the evaluation of the EU Orphan Regulation Final report, 2019). The upward trend is evidenced in the average number of MAs granted in three six-year periods: 3.7 in 2000–2005, 7.8 in 2006–2011, and 12.2 in 2012–2017. Regulation (EC) No. 141/2000 and scientific progress have both contributed to this growth (Study to support the evaluation of the EU Orphan Regulation Final report, 2019).

The investments made have resulted in the introduction of new therapies that have improved the lives and health of 6.3 million MR patients. These new drugs cover major therapeutic areas, providing treatment options for a substantially broader range of conditions than were available before the regulation was introduced. They thus make a useful contribution to addressing the hitherto unmet needs of RDs' patients, including those with ultra-rare conditions. However, and as highlighted in the *Background* section of this *Statement*, in terms of placing treatments on the market in areas with no current viable treatment option, the regulation shows inferior benefits. Furthermore, although the authorized products cover a wide range of therapeutic areas and indications, a particular concentration can be observed in the oncology area. This is due to several factors, including the availability of guidelines, alignment with existing research and development expertise and knowledge, and the availability of other treatment options. There is an increasing tendency to grant conditional access to drugs that address unmet therapeutic needs when the evidence supporting them is not yet sufficiently developed.

Overall, Regulation (EC) No. 141/2000 has helped address some of the unmet needs of MR patients, but the unmet need remains considerable.

Definitions of UMN include situations in which:

- there are no licensed medicines available for a particular MR or disease that affects children, and no other medical treatments (e.g., surgery) are available.
- treatments are already available, but their effectiveness and/or safety is not optimal (e.g., they only address symptoms).

- treatments are available but impose a high burden on patients (e.g., frequent hospital visits for medication administration).
- treatments are available, but not adapted to all subpopulations (e.g., there are no adapted doses and/or formulations, such as syrups or drops for children).
- and more.

It is important to support research efforts aimed at addressing diseases that still lack therapeutic solutions. In the recent past, all RDs lacked solutions, so care must be taken not to create a dichotomy between different diseases.

Proposal

The Forum agrees to avoid including any kind of rigid definition in the revision of Regulation (EC) No. 141/2000 and pediatric, as it risks limiting the concept to something easily outdated over time. Moreover, the concept of UMN is already partly implied when referring to the "significant benefit" provided in the current regulation. This benefit, as seen above, is evaluated both at the early stage of drug development and later at the time of MA: in the early stage, in fact, because of the paucity of evidence (usually for nonclinical data or a small number of patients),the significant benefit is assumed or surmised but not demonstrated; during development, the assumption of benefit may change or diverge from the initial opinion.

It also recommends adopting a generic, high-level definition that allows it to be declined depending on the pathology under consideration.

***How to Define Rarity* (6)**

Background

This paragraph is related to the previous one on UMN.

The measure of rarity varies. Some conditions meet the current prevalence threshold but are not as rare as others. The spectrum is very broad.

The various FMRP discussions have raised questions such as: Is the concept of "rarity" determined by incidence? By prevalence? By the nature of the disease? It is essential to acknowledge that the current OD criteria are effective because they provide a key predictability factor for research. Therefore, it is critical that any alterations not impose restrictive changes. Prevalence as a defining concept is useful for chronic conditions where drug use is lifelong; however, for OMPs, the nature of the disease should be the criterion. It is necessary to distinguish between levels of magnitude of rarity among different diseases. A positive example can be found in oncology, where decisions can be made based on greater need.

What is the definition of an orphan condition? In some cases—mono-causal conditions—the answer is simple. Other cases, where the underlying causes are more complex and where many biomarkers determine the clinical course and change the nature of the condition, pose greater challenges.

Proposal

The Forum agrees not to change the current definitions on the *rarity* threshold.

It reinforces the arguments in the previous paragraphs, that it is necessary to promote and encourage scientific research to give RDs' patients the correct treatment.

***Insights into Pediatric Regulation* (7)**

Background

The EU Pediatric Regulation is structured around three main objectives:

1. Improving children's health by facilitating drug development
2. Improving the availability of drugs with pediatric-friendly formulations
3. Increasing available information on pediatric medicines

Since the inception of Regulation (EC) No. 141/2000, 111 out of 142 medicines (constituting 78% distributed as follows: 68% adult and pediatric indications, 8% pediatric only) have been placed on the market for orphan conditions that also affect children (Study to support the evaluation of the EU Orphan Regulation Final report, 2019). This includes 14 products for exclusively pediatric conditions, while the majority cover conditions that affect both adults and children. In addition, again according to the Study to support the evaluation of the EU Orphan Regulation Final report, as of 2019 there are 56 OMPs approved for use in children, or about 50% of the total. The impact of Regulation (EC) No. 141/2000 has not been as hoped, resulting in a partial and limited effect on the development of drugs with pediatric indication (Study to support the evaluation of the EU Orphan Regulation Final report, 2019; Public consultation factual summary report Impact Assessment-Study supporting the Impact Assessment of the revision of the EU legislation on medicines for children and rare diseases: Consultation outcome, 2021).

Off-label use of drugs in pediatric settings is an approach related to the limited availability of evidence in response to unmet therapeutic needs.

In the development of a drug with a pediatric indication, evidence generation is now commonly supported, after the evaluation of necessary assumptions, through extrapolation, i.e., the use of knowledge/data derived from adult or other pediatric ages to inform drug development and to reduce the amount of new evidence required (EMA, 2018; FDA, 2022).

In addition, it is important to increase the informed and participatory involvement of patients and their families. The incentive provided by Regulation (EC) No. 1901/2006, i.e., the six-month

extension of the ME for drugs with a PIP, was only partially effective.

Proposal

A revision of EMA's methodological framework for PIP is proposed,aiming at a comprehensive development strategy that facilitates the early sharing of information on molecules in development among different *stakeholders* (academia, industry, and regulators). The goal is to enable decision-making on molecule prioritization and study design to include innovative approaches and improve the feasibility and efficiency of PIPs.

In this R&D strategy, the use of RWD, including disease registries and data collected by ERNs, properly designed and evaluated by regulators, should be encouraged. With this objective, the *Data Analysis and Real-World Interrogation Network* (DARWIN EU) was created.

***Harmonization of European Regulations* (8)**

Background

The possibility of generating an effective regulatory environment to promote the development, introduction, and access to safe, effective, and affordable pediatric OMPs and medicines in the European context depends on the level of harmonization of Regulation (EC) No. 141/2000, Regulation (EC) No. 1901/2006 and other EU legislation, including:

- Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU.
- Proposal for a regulation – The European Health Data Space (EHDS), 2022
- Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016
- Regulation (EU) 2017/745 of the European Parliament and of the Council of April 5, 2017 on medical devices
- Regulation (EU) 2017/746 of the European Parliament and of the Council of April 5, 2017 on in vitro diagnostic medical devices
- Directive 2011/24/EU of the European Parliament and of the Council of March 9, 2011 on the application of patients' rights in cross-border health care

Proposal

A strong harmonization exercise is needed, considering the requirements and objectives of the individual regulations, and facilitating their subsequent proper implementation at the European level and their subsequent applicability at the local level.

It is hoped that MS agreements will be promoted to enable equitable access for patients with MR and pediatric patients, allowing for care throughout Europe.

The EU should take charge of promoting understanding among MS by creating a European *network* to strengthen centers of excellence evaluated and approved at the EU level.

Acronyms

AA, *Accelerated Assessment*
AIC, *Marketing Authorization*
AIFA, *Italian Drug Agency*
ALTEMS, *High School of Health Systems Economics and Management*
ATMP, *Advanced Therapy Medicinal Product*
CAT, *Committee for Advanced Therapies*
CHMP, *Committee for Human Medicinal Products*
CMA, *Conditional Marketing Authorization*
COMP, *Committee for Orphan Medicinal Products*
EC, *European Commission*
EEA, *European Economic Area*
EHDS, *European Health Data Space*
EMA, *European Medicines Agency*
ERN, *European Reference Networks*
EU, *European Union*
EUnetHTA, *European Network of HTA*
FDA, *US Food and Drug Administration*
FMRP, *National Forum on Rare and Pediatric Diseases*
HTA, *Health Technology Assessment*
JSC, *Joint Scientific Consultation*
MA, *Marketing Authorization*
MAH, *Marketing Authorization Holder*
ME, *Market Exclusivity*
MS, *Member State*
OD, *Orphan Designation*
OMP, *Orphan Medicinal Product*
PAES, *Post-Approval Effectiveness Studies*
PASS, *Post-Approval Safety Studies*
PDCO, *Paediatric Committee*
PIP, *Pediatric Investigation Plan*
R&D, *Research and Development*
RCT, *Randomized Clinical Trial*
RD, *Rare Diseases*
REA, *Relative Effectiveness Assessment*
RWD, *Real-World Data*
RWE, *Real-World Evidence*
SAWP, *Scientific Advice Working Party*
SME, *Small and Medium-Sized Enterprise*
SoC, *Standard of Care*
UMN, *Unmet Medical Need*

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Xoxi E, Di Bidino R, Leone S, Aiello A, Prada M. Value assessment of medicinal products by the Italian Medicines Agency

[i] Regulatory framework

Regulation [EC] No. 141/2000 of the European Parliament and of the Council of December 16, 1999 on orphan medicinal products offers developers a range of financial and other incentives to encourage investment in OMP development.

To qualify for these incentives, a product should be intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition that affects no more than five in 10,000 people in the EU and would not be economically viable without incentives. In addition, it should be demonstrated that there is no satisfactory therapeutic alternative or that the product offers significant advantages over other available products. All applications are evaluated by a *specially* created body: the EMA's COMP.

If a designated OD meets all requirements at the time of MA, it is granted a 10-year period of ME in the EU. During this period, no other treatment for the same condition will be allowed on the market if it is considered similar.

Other available incentives include fee waivers and access to a special form of *scientific advice* known as *protocol assistance*. Regulation (EC) No. 141/2000 also allows MS and the EU to provide additional research assistance. The centralized procedure for AIC has been deputed to facilitate a single market.

Designation criteria

The criteria for orphan designation are first introduced in Article 3 of Regulation 141/2000, which states that a product is eligible for designation if a sponsor can establish:

1a) that it is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or

1b) that it is intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating, or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment.

The sponsor must also establish:

2) That there exists no satisfactory method of diagnosis, prevention, or treatment of the condition in question that has been authorized in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

Committee for Orphan Medicinal Products

Article 4 of Regulation 141/2000 dictates the creation of a "Committee for Orphan Medicinal Products" (COMP) with the following responsibilities:

- *To examine any application for the designation of a medicinal product as an OMP which is submitted to it in accordance with this Regulation*
- *To advise the Commission on the establishment and development of a policy on OMP for the EU*
- *To assist the Commission in liaising internationally on matters relating to OMP as well as in liaising with patient support groups*
- *To assist the Commission in drawing up detailed guidelines*

It further specifies that the COMP shall comprise:

- *A chair, elected by serving COMP members*
- *One member nominated by each MS (currently 28)*
- *Three members appointed by the EC on the Agency's recommendation.*
- *Three members representing patient organizations nominated by the EC.*
- *Representatives of the Commission and the Executive Director of the Agency or his representative may attend all meetings of the Committee.*

At present, the COMP also contains members appointed by Iceland and Norway. COMP members are appointed for a renewable term of three years. The composition and tasks of the COMP are laid down in its Rules of Procedure.

Procedures for designation and removal

The procedures for designation and removal from the register of OMP are laid down in Article 5 ofRegulation 141/2000. Parties seeking to apply for an orphan designation can either submit their application directly or request a pre-submission meeting to informally discuss the draft application and obtain feedback from the coordinators on likely weaknesses in the application. 21 Hereto, one week before these meetings, a draft application should be submitted. Once submitted, the applications are reviewed by the COMP. The COMP can decide to invite the applicant to provide an oral explanation at a COMP plenary meeting. It should adopt an opinion within 90 days. When a negative opinion is deemed inevitable, the applicant is given the opportunity to withdraw the application. The applicant also has the option to appeal a negative opinion. After the COMP has adopted its opinion, the EC has a further 30 days from receipt to issue a decision.

Centralized authorization procedure

Article 7 of Regulation 141/2000 gives sponsors access to the centralized authorization procedure that grants the marketing authorization holder (MAH) the right to bring a product to market in all EU countries at the same time22. Initially, access to this procedure was optional, but with the adoption of Regulation (EC) No 726/2004, the centralized authorization procedure became mandatory for all designated orphan medicines.

Incentives

The Regulation introduced a comprehensive set of tools to incentivize developers of medicinal products at various points throughout the R&D pathway, from the early stages of research to placing a product on the market. These comprise:

- *ME (Article 8 of the EU Orphan Regulation), which creates for the MAH an additional temporary exclusivity right (in addition to the regular protection of medicinal products).*
- *Protocol assistance (Article 6 of the EU Orphan Regulation), which offers the sponsor of a designated orphan medicine the option of requesting advice from the EMA on the tests and trials necessary to demonstrate the quality, safety, and efficacy of the medicinal product.*
- *Fee waivers (Article 7 sub 2 of the EU Orphan Regulation), which offer total or partial exemption from the payment of fees for applications for designated orphan medicines. Typical fees for MA applications start at €291,000, with annual fees of around €104,600.*

- *Aid for research (Article 9 of the EU Orphan Regulation), which makes it possible to create other incentives to stimulate the development and marketing of orphan medicines, at the level of the EU or individual MS.*

A series of guidelines, notices, and implementing regulations have also been developed in parallel with the EU Orphan Regulation, which together form the regulatory framework.

Evolution of the EU Orphan Regulation

Regulation 141/2000 laid down the Community procedure for designating orphan medicines, providing R&D incentives, and placing designated orphan medicines on the market. As such, it forms the basic framework for what is referred to as the "EU Orphan Regulation." However, the original Regulation identified several follow-up actions required to effectively implement the Regulation. Specifically, it stated:

- *In consultation with the MS, the Agency, and interested parties, the Commission shall draw up detailed guidelines for the form in which transfer applications shall be made and the content of such applications and all the particulars of the new sponsor. (Article 5.11)*
- *The Agency shall draw up a procedure on the development of OMP, covering regulatory assistance for the definition of the content of the application for authorization within the meaning of Article 6 of Regulation (EEC) No 2309/93. (Article 6.2)*
- *The Commission shall adopt definitions of "similar medicinal product" and "clinical superiority" in the form of an implementing Regulation. Those measures, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 10a(3). (Article 8(4))*
- *The Commission shall draw up detailed guidelines for the application of this Article in consultation with the MS, the Agency, and interested parties. (Article 8(5)).*

Other follow-up actions:

- *Implementing Regulation, No 847/2000*
- *2006 Paediatric Regulation is a case in point, which created the possibility for orphan pediatric medicines to be granted two additional years of ME.*
- *Key developments, cross-referencing the amendment or additional guidance to the original Regulation:*
    - *Criteria for designation: Commission Notice 2016/C 424/03*
    - *Centralized procedures: Regulation (EC) No. 726/2004*
    - *Fee reductions and exemptions for SME: Regulation (EC) No. 2049/2005*
    - *CMA: Regulation (EC) No. 507/2006*
    - *Extension of ME for orphan pediatric drugs: Regulation (EC) No. 1901/2006*
    - *Clarification for COMP procedure: Guideline 2008/C 242/07*
    - *Commission Notice 2016/C 424/03: Criteria for designation.*
    - *Commission Regulation (EU) 2018/781: Concepts "similar medicinal product" and "clinical superiority"*

[ii] Since the Implementation of Regulation (EC) No. 141/2000:

For a product to be granted OD it must also be demonstrated that "there is no satisfactory treatment for the condition in question in the EU, or if there is, the product in question will be of significant benefit to patients affected by that condition." The EU Orphan Regulation thus requires a sponsor to provide details of "existing methods, which may include authorized medicinal products, medical devices, or other methods of diagnosis, prevention or treatment, which are used in the Community [European Union]."

Existing methods: Only authorized products should be considered. Non-pharmacological methods could be considered as a satisfactory method. In certain cases, "magistral formulae" and "officinal formulae" may be considered as satisfactory treatment if they are well known and safe and are in general practice in the EU.

A product can be said to provide significant benefit if it confers a clinically relevant advantage or offers a major contribution to patient care over existing authorized medicinal products or methods at the time of designation.

[iii] Some definitions on unmet clinical need from various authorities involved are given here:

Unmet Medical Need (UMN) - Definitions, ranking et al.,
A **condition** whose treatment or diagnosis is not adequately addressed by available therapy. A UMN includes an immediate need for a defined population (e.g., to treat a serious condition with limited or no treatment) or a long-term need for society (e.g., to address the development of antibacterial drug resistance). No *ranking* *Setting*: US regulatory (Source: FDA Guidance for Industry. Expedited Programs for Serious Conditions–Drugs and Biologics [FDA 2017a])
A condition for which there is no satisfactory method of diagnosis, prevention, or treatment in the EU, or even if such a method exists, in relation to which the drug in question will be of great therapeutic benefit to those affected. No *ranking* *Setting*: EU regulatory (Source: Article 4 paragraph 2 of Commission Regulation (EC) No. 507/2006 [about conditional marketing authorization]) *Orphan Designation - A product is eligible if a sponsor can establish:* 1. *that it is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or* 2. *that it is intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating, or serious and chronic condition in the Community and that without incentives it is unlikely that the marketingof the medicinal product in the Community would generate sufficient return to justify the necessary investmentAND,* 3. *That there exists no satisfactory method of diagnosis, prevention, or treatment of the condition in question that has been authorized in the Community, or if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.* (Source: Designation criteria Art. 3 of Reg 141/2000) *Orphan condition: any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognized distinct disease or a syndrome) that meets the criteria defined in Article 3 of Regulation (EC) No 141/2000* *Orphan indication: the proposed indication for the purpose of orphan designation. This specifies if the medicinal product that is the subject of the designation application is intended for diagnosis, prevention, or treatment of the orphan condition.* *Therapeutic indication: at the time of the orphan designation application, the sponsor proposes a therapeutic indication. The therapeutic indication granted at the time of MA will be the result of the assessment of the quality, safety, and efficacy data submitted with the MA and may be different from that initially proposed. The therapeutic indication can also be changed or expanded after MA based on new clinical evidence.* (Source: Implementation of Reg 141/2000)

Therapeutic Need (assessed by single therapeutic indication) is conditioned by the availability of therapies for the condition in question and indicates how much the introduction of a new therapy is necessary to address the therapeutic needs of a patient population.

Si *ranking:* Five levels from highest to lowest
Setting: HTA/ national payer Italy

(Source: AIFA Determination No. 1535/2017 on the classification criteria for innovative drugs and innovative oncology drugs pursuant to Art. 1 Paragraph 402 of Law No. 232 of December 11, 2016)

HTA approach

1. Elements of *UMN*
2. Stakeholder considerations for *UMN*
3. A proposal: population or patient perspective
4. Proposal for a staggered approach to UMN-based assessment of HT by decision-makers. *The elements considered are not exhaustive and depend on the decision-maker. Three categories include adequacy of alternative treatments, disease burden, or population size.*