

# Conference "Medicines for Rare Diseases and Children: Learning from the Past, Looking to the Future"<sup>1</sup>

Brussels, 17 June 2019

## Report

### Introduction

A conference entitled "Medicines for Rare Diseases and Children: Learning from the Past, Looking to the Future" took place on 17 June in Brussels. The event, organised by the European Commission's DG SANTE, brought together some 150 experts from across the EU, representing national governments and health authorities, academia, patient and health professionals' organisations and the pharmaceutical industry.

The background to the event relates to two EU Regulations, i.e. on Orphan Medicinal Products (2000) and Paediatric Medicines (2006). The ultimate objective of these two pieces of legislation was to increase therapeutic choices for patients suffering from rare diseases and children by bringing more medicinal products for those therapeutic areas to the market.

Following the publication of a 2017 Commission Report on the Paediatric Regulation, the European Commission announced a joint evaluation of the Regulations in order to assess their effects and impacts to date.

This conference was organised to offer stakeholders the opportunity to make their voices heard and come forward with their views, suggestions and ideas with respect to the two Regulations.

The conference's interactive format allowed participants to make their voices heard. Methods of Participatory Leadership were used, thereby directly involving all participants in the discussions and benefiting from the collective intelligence in the room.

- In the morning, 5 break-out sessions took place, during which the following topics were addressed: unmet medical needs, incentives, medicines for children, from R&D to patients and scientific developments.
- An 'Open Space' session, taking place in the afternoon, provided participants with the opportunity to propose topics they wanted to address and to run little workshops on their topic with interested delegates.

### Opening plenary session:

Moderator **Professor Patrick Deboyser (European College of Parma)** welcomed participants and provided a brief overview of the programme and its aims, i.e. to bring stakeholders together for an open and frank discussion about the state of play - successes, shortcomings, potential - of the Orphan and Paediatric Regulations.

Professor Deboyser then introduced Health Commissioner **Vytenis Andriukaitis**, who underlined that progress has been made with respect to improving access to medicines for children and rare diseases. However, more should be done and activities should be expanded.

Commissioner Andriukaitis briefly spoke about the EU Orphan Regulation (2000) and the EU Paediatric Regulation (2007), stating that it is also important to take a critical look at these Regulations. Called on by the Council to do so, the Commission decided to jointly evaluate the two Regulations. The aim is to finalise this process by the end of 2019; the findings will serve as a base for the next Commission to reflect on the need for and nature of follow up actions.

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<sup>1</sup> Disclaimer: views expressed at the conference are those of the participants and do not necessarily represent the official views of the European Commission.

Commissioner Andriukaitis also shared some insights from recent studies regarding orphan and paediatric medicine and pharmaceutical incentives in general, such as the Commission 2017 report on Paediatric medicines and the 2018 study on the impact of pharmaceutical incentives. He announced that a study on the functioning of the EU Orphan Regulation will be published later this year. All studies and public consultations have revealed substantial differences in the level of access to affordable treatments, between as well as within Member States resulting in fundamental health inequalities. In order to address this issue a higher level of commitment is required from all players to improve the availability and affordability of therapies across the EU. The Commissioner also touched upon the new Horizon Europe program, which will support possibilities to tackle some of the shortcomings highlighted<sup>2</sup>.

The next speaker was **former Member of the European Parliament Françoise Grossetête**, addressing the audience via video messaging.

Mrs. Grossetête emphasised the importance of the Regulations on Paediatric and Orphan Medicines; these have addressed real medical needs and have been at the basis of a number of therapeutic breakthroughs. Of course, there are weaknesses that need to be addressed – this conference can help identify the challenges and best ways forward.

The two Regulations can indeed be looked at in parallel as there are many interconnections and it is useful to assess where and how the two pieces of legislation could work better together.

She also felt that it would be interesting to analyse why the incentives for the development of Orphan and Paediatric medicines are not used more frequently and why they do not stimulate more research; despite the success of the Regulations, the level of unmet needs remains high. While the number of treatments has increased in the area of rare disorders, only 5% of those living with a rare disorder can be treated; that means that for 95 % no treatment options are available. However, this does not mean that the Orphan Regulation is not delivering; it merely underlines that R&D in this area is highly complex and that Regulations are not the only solution. Patients registries can help improve data collection and analysis. The European Reference Networks (ERNs) have also proved to be extremely useful in generating data and cooperation in this area.

In conclusion, Mrs. Grossetête urged participants to be careful not to undermine the existing Regulations and carefully address regulatory barriers. Issues related to patient access will not be solved by a piece of legislation alone. Also, access to medicines remains a Member State competence. For Mrs. Grossetête, this does not really make sense; change and progress will be hard to effectuate if Member States are not willing to cooperate further.

**Professor Deboyser** reminded the audience that the two Regulations, at the time of their adoption, represented a true paradigm change in relation to the EU level pharmaceutical legislation: until the adoption of the Orphan Regulation, this legislation mainly concentrated on harmonisation and creating a single market for pharmaceuticals. However, as the Treaty on European Union stipulates that ‘a high level of human health protection shall be ensured by all Community Institutions in the definition and implementation of all Community policies and activities’ there is room for a more public health-oriented approach. This approach can be seen in the Orphan and Paediatric Regulations.

It is now time to check if these two pieces of legislation still serve better access of patients living with rare diseases and children. That should be the standard for measurement of progress in the conference’s discussions.

**Professor Deboyser** then introduced **Olga Solomon (Head of DG SANTE, Medicines: policy, authorisation and monitoring)** and **Michael Berntgen (Head of Product Development Scientific Support Department, EMA)** who jointly set the scene for the conference and the discussions ahead.

*Olga Solomon* focused on the past EU level policy and regulatory activities in the field of orphan and paediatric medicine as well as on the feedback obtained from the ‘real life’ application of the two Regulations.

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<sup>2</sup> For the full speech of the Commissioner:

[https://ec.europa.eu/commission/commissioners/20142019/andriukaitis/announcements/medicines-rare-diseases-and-children-learning-past-looking-future\\_en](https://ec.europa.eu/commission/commissioners/20142019/andriukaitis/announcements/medicines-rare-diseases-and-children-learning-past-looking-future_en)

Rare diseases comprise between 6.000 and 8.000 life threatening or chronically debilitating diseases which affect less than five persons per 10.000 citizens in the EU. It is estimated that rare diseases affect more than 30 million people in the EU alone (i.e. 6 - 8% of the EU population). The impact on the quality of life of affected patients -many of them children- and their families is significant.

In 2000, the EU came forward with the Orphan Regulation, with the objective to provide incentives for the research and development and market placement of orphan medicines, ensuring the same level of access to quality treatment for patients living with rare conditions as other patients. In 2007 the EU Paediatric Regulation was introduced to improve the development of high-quality medicines for children.

Market failure was the common ground for both areas, as pharmaceutical companies were reluctant to invest in the development of innovative medicines for small numbers of patients.

The Orphan Regulation establishes a two-step process i.e. designating products at the development stage as orphan medicines and subsequently granting exclusivity rights once the product is authorised. This allows developers to secure R&D financing either through the EU research framework or national funding mechanism and also to attract private investors more easily. Once the development is completed a company can apply for an EU wide marketing authorisation. An authorised orphan medicinal product will enjoy a monopoly period (market exclusivity) of 10 years. This can be extended to 12 years if a Paediatric Investigation Plan (PIP) is completed.

The Paediatric Regulation is structured around three main objectives:

- more research into the development of high-quality medicines for children.
- more authorisations with age-appropriate forms and formulations.
- more information in the product summaries about medicines used by children.

To meet these objectives, the Regulation has set up a system of obligations, rewards and incentives. It also comprises measures to ensure that medicines are regularly researched, developed and authorised to meet the specific needs of children. It is based on the idea that a company should be obliged to screen every product it develops for its potential use in children, thereby progressively increasing the number of products with paediatric indications.

Progress has been made since the Regulations came into force. However, only some 5% of identified rare diseases have so far been addressed under the Orphan Regulation. The pharmaceutical industry claims that without incentives the development of new treatments for rare diseases will slow down. Some weaknesses have also been identified as regards the Paediatric Regulation: these mainly relate to the incentives provided for the development of these medicines. The general effectiveness of the system to address unmet needs and achieve availability and equal patient access across the EU can also be improved.

*Michael Berntgen* then provided the EMA perspective as well as some initial thoughts in relation to the two Regulations. Like previous speakers, he underlined the timeliness of the conference as the opinions, suggestions and critical remarks will feed into future reflections on the regulatory framework of these areas.

In terms of orphan medicines there are several issues for reflection. For instance, what is the definition of an orphan condition? In some cases – monocausal conditions – the answer is simple; but other cases, where the underlying causes are more complex and where many biomarkers drive the clinical course and change the nature of the condition pose more challenges.

He wondered whether the same prevalence would be relevant in all circumstances and if advanced therapies are increasingly being developed in this space. How can benefit be demonstrated and where is the value?

In terms of paediatric medicines, key issues relate to the early agreement of the PIPs. These Plans need to be realistic and workable. There have to be acceptable designs for the process of clinical trials. Discussions with the respective stakeholders are needed. Since a new policy on waivers has been introduced a number of changes can be seen: there is a larger number of PIPs with broader indications; there is more discussion with stakeholders, as a basis for shaping developments. There is more space for the necessary scientific discourse in the interest of patients.

All these elements are the subject of today's debate: how to apply the concept of 'significant benefit', what are the hurdles and barriers, what are the expected scientific advances? The March 2018 EMA/European Commission Paediatric Action Plan is now being implemented; this conference will also help progress this Plan.

There is a collective responsibility of all stakeholders to identify medical needs and reflect on how to address these. A shared vision will help to define the way forward.

**Three questions for the audience to answer:**

- *How ready are you to brainstorm on the Orphan and Paediatric Regulation today?*  
The majority of the audience responded **positively** to this question.
- *What is the pace of development of the Orphan and Paediatric Regulation since their adoption, dog, turtle or cheetah?* The majority felt **'dog'** was the answer.
- *Which word comes to mind when you think of the Orphan and Paediatric Regulation?*  
Many different words were proposed, with frontrunners **'innovation', 'essential', 'incentives', 'hope' 'unmet needs' and 'complicated'**.

### **Break-out sessions**

Following the plenary introductions participants broke into 5 working groups, addressing unmet medical needs, incentives, medicines for children, from R&D to patients and scientific developments respectively. Engaged discussions took place on the basis of 3 guiding questions per topic (see Appendix). In each break-out session, participants representing different views were divided into small groups to discuss the problem formulation, solutions and possible way forward on each sub-question, like this everyone had an opportunity to contribute to each topic. At the end, a rapporteur assigned to each break-out sessions, reported briefly to the plenary on the main points discussed.

### ***Unmet Medical Needs***

The EU Regulation on conditional marketing authorisation provides a definition of Unmet Medical Needs (UMN); However, whether it is understood in the same way by all involved parties, it is not certain. For example, if a treatment for a specific condition is not a cure, there is still an unmet medical need. In this context, the value of input from 'expert patients' was considered helpful for the definition of UMN; quality of life and other patient reported outcomes are relevant and should be actively sought and included. Quantifying UMN would also be helpful, as this could translate into direct benefit for patients. Moreover, any efficacious treatment used for the patients should be able to define the UMN.

It was also remarked that a broader understanding of UMN could serve both paediatric and orphan medicines development. In addition, designation of a medicine as an orphan medicine could be granted very early in the development stage – even at the concept stage. This could be combined with compulsory collaboration and information-sharing with respect to pre-competitive elements such as endpoints, medical history etc.

The potential impact of tax and fees incentives on investment in areas of unmet medical need, especially in relation to ultra-rare diseases (where the current level of interest and action is low) was also discussed. A robust analysis of the current state of play would help to determine the balance between incentives and rules. Different levels of incentives might be required, for example for the development of areas where no treatment is yet approved. In this respect, it might also be considered to discourage the development of medicines if their potential benefit is incremental rather than significant; however, medicines of which the benefit is incremental do offer the benefit of more options for patients.

It was also noted that the existing legal framework would have led to the development of areas which are already 'crowded' with possible treatments.

The importance of global cooperation and data sharing, in order to facilitate the development of medicines addressing unmet medical need - especially in the area of medicines for children – was considered important. However, the different regulatory frameworks in place across the world can hinder this type of cooperation.

Other points raised related to the need to foster a better understanding of off-label use and compounding needs, the challenges of implementing the orphan criteria as set in the Regulation and to who should set the

bar. In any case, it was agreed that the benefits of medicines need to be determined on a case-by-case basis even though this may be difficult in the area of rare diseases. Finally, the need for the scientific journey of a product to be reflected in its price was also addressed.

### ***Incentives***

The two Regulations were considered successful in supporting innovation; however, they may not be focused enough as the increase in the numbers of new medicines does not necessarily mean that societal needs are being properly addressed. In addition, the connection between financial reward and the cost of the development of a medicinal product may not always be clear. It would be important for any financial reward scheme to incorporate the entire life cycle of a product.

This links in with the prominent issue of affordability and accessibility of medicine; the relationship between costs and results should be proportional and transparent. As part of this discussion, it was remarked that any regulation should encourage competition and a combined approach of price level control and incentives for 'smaller' medicines. It needs to be borne in mind however that financial rewards and incentives are not the only solutions to improve the situation; there can be others, such as stimulation of basic research, the use of patient vouchers etc.

It was also discussed that the logic introduced by the EU Orphan Regulation has had a positive effect avoiding market failures for orphan medicines. However, market exclusivity should be part of a holistic protection system that links to horizon scanning, value of the expected outcome and frequent re-assessments.

Other remarks focused on the need to slightly adjust and/or differentiate the Regulations to ensure a better management of market exclusivities vis-a-vis a fair market access for all companies, also smaller ones. Moreover, the existing incentives (at national and other levels) may not be in harmony; how could these be streamlined to ensure a stronger focus on where society wants these investments to be made?

The concept of 'value' was also addressed. Should the financial rewards be linked to the cost or to the value of a product? How is the value of a product to be determined? One important element of the solution could be to actively involve relevant stakeholders in discussions relating to the societal value of medicines.

Furthermore, what to do about failure of innovations, as investment does not always yield positive outcomes? The question who would bear the risk of those failures came up: would it be society or the individual companies involved?

Other issues identified related to the need to prevent misuse of the Regulations, to better coordinate and identify the priorities and incentivise the collection and sharing of data.

### ***Medicines for children***

Participants underlined that, currently, the development of medicines for children is mainly adult-driven; and that the so-called 'return on investment' (ROI) is an important factor. While there are new ways of promoting science for children financial aspects come into play.

Another fundamental challenge relates to the lack of knowledge with respect to medicine development for children, both in terms of physiology and the development process itself. Clearly, the scientific knowledge about medicines development in such small populations needs to be advanced; but this is challenging in many areas, such as limited number of patients that can participate in clinical trials. Therefore, it was suggested that an overarching, multi-disciplinary R&D strategy should be put in place, supported by appropriate disease registries, with the aim to develop paediatric-only medicines. The collection of minimum data sets could help foster those medicines. In addition, a financially independent, global-level platform could be helpful to promote the development of paediatric medicines. Initiatives such as the Innovative Medicines Initiative (IMI) were considered useful but are more focused on basic research.

Discussions also addressed the concept of ‘Orphan-like’ designations: this applies to conditions which do not meet the criteria to be considered as orphan, but where small subpopulations require a special formulation. The question how these can be best catered for came up.

With respect to the two Regulations it was noted that these do interact; however, they need to be better aligned in relation to the definitions they provide on major concepts (e.g. ‘benefit’) as well as on rewards and incentives. A review of these issues would be helpful.

Other points focused on ensuring that the designation of a medicinal product as ‘orphan’ should not hamper other designations, revisiting the advantages of collaboration for reinvestment and working with paediatric ‘masterplans’. These should ensure the inclusion of all stakeholders as already happening in certain therapeutic areas.

### ***From R&D to patient***

Many hurdles in translating research findings to benefit patients still exist, such as academia not having sufficient knowledge of regulatory requirements and incentives. Moreover, how to define the most relevant endpoints is also challenging; these issues result in lack of information and uncertainties for other stakeholders, such as patients.

Participants suggested ways to better address these hurdles, such as increasing the efforts in the basic research area with respect to many of the orphan and paediatric pathologies, as well as sharing and dissemination of studies, data and information. Early dialogue between all players involved would also be beneficial. In addition, the development of models, providing incentives to academia and Small and Medium-sized Enterprises, such as Public Private Partnerships (PPPs), could be helpful. Other useful models already exist, such as the ERNs, involving many players; this could be rolled out to other areas of research.

The discussion also addressed the lack of a shared strategic vision when it comes to investment in research and unmet needs. This is leading to duplication of research efforts and investment as well as to a lack of transparency. Horizon scanning could help to prioritise research needs, and could feed into the development of roadmaps to steer and coordinate national and EU level research activities. PPPs could also play a role. In this context, there should also be greater transparency with respect to public research funding and findings; business models should better reflect public investment and its benefits.

On data, it was underlined that real-world evidence should focus on overcoming the lack of inconsistent data availability and the development of standardised infrastructures. Currently, too many players are working in silos; the quality and compliance of available data is inconsistent. Moreover, the relatively new EU General Data Protection Regulation (GDPR) and the different ways in which this legislation is interpreted creates new hurdles. It would therefore be helpful for the Commission to issue guidelines supporting a consistent interpretation of GDPR; this could also support data sharing.

Other aspects addressed related to the need for more guidance by EMA and EUnetHTA, the need for a central body to collect and standardise data (the ERNs could serve as a model) and the importance of registries and core, condition-specific datasets as important sources of information; these will need continuous public funding.

### ***Scientific development***

Data and evidence generation were considered crucial to increase opportunities for a better understanding and treatment of diseases. Data complexity also needs to be more effectively managed; and existing data should be put to better use and generated for other users. All available information – from national, EU and global initiatives – should be increased and shared. Horizon Europe could play an important role in this respect. However, there are questions with respect to the ownership of information. Who would be able to decide on who would share what data?

In terms of data policy and acceptability of evidence for decision making, the environment keeps changing; given the wealth of data generated there is a case for a solid infrastructure to better process this information. Multi-stakeholder engagement is needed to overcome the changing evidence standards, taking account of scientific

advances. In addition, it should be known earlier what evidence is needed in order to have informed discussions with regulators and decision makers at later stages in the process. In this respect it is also relevant to bear in mind follow-up developments such as generics, biologics and biosimilars. How will these be affected by current regulations, especially in the orphan space? How to facilitate comparability exercises in this area? Is there a need to look closer at the evidence base?

Other aspects were touched upon: these included the case for a stronger link between genetic sequencing, biological data and outcomes; the possibility of decentralised clinical trials (which should be patient outcome-led and make use of existing qualification systems); the importance of incentives to stimulate voluntary PIP submissions; the potential usefulness of data and evidence gathered in compassionate use programmes; the need to mandate evidence generation plans and the need to revisit the definition of 'orphan medicine' (this is perhaps not just about the condition or prevalence but rather the number of patients that can be treated). The regulatory framework and implementation need a balance between core legislation and supplementary acts, in order to be adaptable and flexible. Finally, it was suggested that, within EMA, there should be better cross-committee operations, possibly even ad-hoc structures reporting back to the various permanent groups.

### **Open Space discussion**

The afternoon Open Space session aimed to provide the opportunity for participants to come forward with specific issues and run little workshops on these topics. A total of 8 topics was discussed as follows:

#### **Making better use of shelved medicines (Proposed by KickCancer)**

The untapped potential of shelved compounds needs to be seized. Transnational harmonised clinical trial procedures need to be put in place, with transparency on ongoing work and those compounds that are shelved – these can be 're-purposed' and be useful for other indications. It is a societal duty to recycle halted compounds for new target populations and facilitate access where possible.

There is no current library of shelved compounds. It could be interesting to track every individual compound and offer companies incentives to hand over stock compounds. It could be seen as Corporate Social Responsibility practice to ensure that compounds that are no longer relevant for a company can be made available to others.

How to improve access to these shelved compounds and transfer them seems quite complicated at the moment. Transfer could be costly – and companies are reluctant to invest in shelved compounds as they no longer serve a purpose. It might be useful to have an open consultation on this topic to determine its relevance as well as the way forward.

#### **How to avoid evergreening (Proposed by European Public Health Alliance)**

The Orphan and Paediatric Regulations offer practical incentives for medicine development. However, this can lead to 'evergreening'; this needs to be avoided.

How can generic and health competition be facilitated? Could there be a clawback mechanism, to be used to stimulate the development of orphan medicines?

How should the clauses in Articles 8(2) and 8(3) of the Orphan Regulation operate, making sure that there are safeguards in place to avoid misuse or profiteering from the Regulations?

This is a sensitive and controversial topic as it relates to a disconnect between pricing and the regulatory remit (between EMA and regulatory authorities)

The criteria for orphan medicine designations are strict. Is science decoupled from regulatory affairs and if not, should it be decoupled? How can science be translated into policy?

How are priorities being determined? The meaning of 'approval' and 'designation' needs to be clear. There also has to be a link between the profits for the developers and the objectives of the legislation.

Positive examples: there are many products entering the market, even loss-making ones; this means that the high profits of other medicines can pave the way for those loss-making medicines to remain in the market.

How is 'profit' defined? There should be equal opportunities for generic medicines; too many generics never make it to the market.

Article 8(2) of the Orphan Regulation is ill conceived and therefore difficult to implement in practice. The predictability for originators and generics should be improved. Issues relating to return on investment should not be examined by EMA, but by some other entity.

### **Global harmonisation/coordination (Proposed by European Society for Paediatric Oncology)**

The presenter clarified that it was decided not to talk about harmonisation as that relates to lengthy ICH<sup>3</sup> processes – which is not required at this point. An innovative stakeholder approach is needed if the speed of R&D is to be increased. Global stakeholder cooperation and development is required – and this also calls for a global regulatory environment. Some positive current examples were given, e.g. the International Rare Disease Research Consortium, the Brighton Foundation (vaccines).

The Orphan Medicines Regulation was a success in several areas; however, neglected areas do remain and need to be addressed. The real needs of patients (particularly children) should be the guiding principle in this respect. A multi-stakeholder approach is required for robust medicines development, ensuring a high-level of market protection to facilitate company investment in these areas. How can regulatory regimes be facilitated and implemented, also taking into account medicines development in low- and middle-income countries?

The coordination between funding sources as well as between existing regulatory bodies should be improved.

### **Innovation and the aeroplane analogy (Proposed by Novartis)**

Pharmaceutical innovation can be compared to creating new ways of flying rather than to developing a new aeroplane. Learning to fly is a gradual process. And so is innovation: this relates to a gradual and progressive building of knowledge of diseases, followed by development of a treatment, based on this understanding. It is an evolution – learning is incremental.

The content of the development and learning process is different for all individual products; the development pathway is unique. The same building blocks can be (re)-used but the ideas behind those building blocks and related processes are brand-new.

Basic research is required as a matter of urgency as new ways to fly are indispensable. New approaches to diseases and innovation have to continue, despite errors and failures.

### **The continuum of evidence generation (Proposed by Eurordis)**

More account should be taken of the continuum of evidence generation as people living with rare diseases are not a homogeneous group; this is simply not the reality.

We need to go from early dialogue with all stakeholders at all stages of development and implementation, from scientific advice to patient input (on needs as well as on outcomes) to regular re-assessment after-market authorisation, checking each step of the way for relevance and breaking through the silos of the various stakeholders involved.

Can the current legislation deliver on this requirement?

The dialogue regarding evidence and scientific advice is scattered; scientific assessment for approval and HTA of a medicine take place in different silos. The complexity of the products and the processes remain challenging. There is a lack of data-sharing as well as a lack of understanding of the work and (potential) contribution of the various stakeholders.

There are some ongoing positive developments, such as early dialogue between HTA and EMA and the workshops organised by the EMA bringing together the various players and facilitating exchange, fostering mutual understanding. The ERNs and the Big Data Taskforce are also positive examples of cooperation.

Engaging patients in discussions about what is meaningful for them and data collection remains a challenge.

### **Value-based pricing (Proposed by EFPIA)**

Pricing can be considered as the ‘elephant in the room’. How to set fair prices? What does the concept of ‘value-based pricing’ mean, to industry and other stakeholders?

Who wants to pay a high price for something that is not of value? And what value to whom? Who decides what the value is – first and foremost for patients but also for payers? Should this be a multi-stakeholder decision?

Clear pricing decisions should be taken at an early stage of the development of a medicine so that investors know what to expect in terms of value and uptake by health care systems. In addition, any decision on pricing should be evidence based.

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<sup>3</sup> International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use



Some positive examples exist, such as ‘managed entry agreement’, ‘price for performance’ and ‘value-based tier pricing’ but how can these systems be introduced into existing health systems? Moreover, value can change over time - so product reviews will be required at regular intervals. Can data sharing help keep prices down? A multi-stakeholder coalition to better understand data and the various stages of the development process will help.

#### **How is ‘rarity’ determined? (Proposed by COMP member/BfARM )**

Is the concept of ‘rarity’ determined by incidence? By prevalence? By the nature of the disease?

The measure of rarity varies. Is a condition ‘rare’ or ‘specialist’? Some conditions do fulfil the current prevalence threshold but are not as rare as others. The spectrum is too broad.

Prevalence as a defining concept is helpful for chronic conditions where the use of the products is lifelong; but, in relation to orphan medicines, the nature of the disease should be the criteria.

There is a need to differentiate between levels of magnitude of rarity across the different diseases. A positive example can be found in the area of oncology, where decisions can be taken on the basis of higher need.

The definition of rare diseases, as used in the current legislation, needs to be reviewed; exceptions need to be possible for specific types of diseases.

A longer period of market exclusivity could be offered for the development of very rare diseases.

#### **More targeted treatments for children’s medicines (Proposed by ERN EPICARE)**

More treatments are needed for children. The reasons why there are so few specific medicines for children need to be looked into. One of the reasons is the lack of knowledge of the aetiology of specific conditions in children; the causes of these diseases should be investigated by means of targeted research. Some positive examples can be found, for instance in the area of Spinal Muscular Atrophy (SMA).

The small numbers of patients are also challenging, as that can be a reason for companies not to invest – this leads to neglected groups of patients.

Financial support will be crucial to stimulate development; data sharing at the pre-competitive stage of development is also important.

#### **Conclusions**

**Professor Patrick Deboysier** expressed his appreciation of the interactive format of the conference, as this supported the broadest level of stakeholder involvement and helped to collect as many views and suggestions as possible. He also provided some of his personal views in relation to the two Regulations, stating that the Orphan Regulation does not address neglected diseases in less-developed countries. However, there has to be a way in which work in this area can be supported. The idea of vouchers (as they exist in US) was not discussed in detail during this conference; however, this idea could be interesting to explore further.

While large parts of the two Regulations work well, there clearly are issues that need improvement, such as Article 8(2) in relation to the period of market exclusivity of orphan medicinal products.

Professor Deboysier concluded by underlining the crucial need for globalisation in relation to orphan and paediatric medicine development; global collaboration will be absolutely vital if real progress is to be made, both in terms of number of products developed as well as in terms of product development speed. It might be worthwhile to organise an international conference on rare diseases and medicinal products in this context.

**Anne Bucher (Director General, European Commission, DG SANTE)** underlined the timeliness of the conference, as the suggestions and views put forward will be part of the reflection process regarding the two Regulations. She also emphasised her personal interest in the topic and confirmed that the conference provided an opportunity for the Commission to listen and take account of stakeholder views. A wealth of ideas has been generated that will inform the next steps as this is the time to reconsider the goals of the Regulations.

The Orphan and Paediatric Regulations had similar objectives, i.e. to make a positive contribution to a neglected field, to meet unmet needs and to improve access to and affordability of medicines. And some progress has indeed been made: a greater understanding of the specificities and the medicinal needs of children has been effectuated. Paediatric clinical trials are considered as essential. Pharma companies have developed more in-house paediatric expertise; patient representatives play a strong role and are also represented within the relevant bodies of the EMA.

However, and as highlighted throughout the conference, important weaknesses remain and need to be addressed. For instance, the development of paediatric medicinal products is still highly dependent on the pharmaceutical pipeline for adults. More specific R&D is required. In the case of orphan medicines, there are still fundamental challenges with respect to accessing these products across the EU, both in terms of costs as well as in terms of availability. This has significant implications for patients and their families.

The concept of 'unmet needs' requires a better definition; moreover, it would be helpful to quantify these needs. A common understanding is required to enable a true assessment of the situation.

In relation to incentives, these have been successful in addressing market failure; however, it has also been argued that they have led to overcompensation. In addition, there is a strong focus on the need to increase and improve data collection and data sharing, particularly where medicinal products for children are concerned.

The scientific understanding of children's diseases needs to be increased and the speed of product development should be stepped up too. There is a need for basic research; and the long pathway to delivery needs to be shortened in order to overcome inequalities.

Anne Bucher warmly thanked the moderator and all participants and concluded that the conference had made a useful contribution to the evaluation. This evaluation will provide the next Commission with a solid piece of evidence and a good basis for future reflection. This event should be considered as the start of a process; stakeholders can look forward to more collaboration in the future.

**Appendix 1: Conference agenda:**

**08:45–09:30**    **Registration and welcome coffee**

**09:30–09:35**    **Opening of the day**

*Professor Patrick Deboyser (European College of Parma)*

**09:35–09:55**    **Keynote opening speeches:**

*Vytenis Andriukaitis - Commissioner for Health and Food Safety*

*Françoise Grossetête - former MEP*

**09:55–10:10**    **Scene setter for medicines for children and rare diseases**

*Olga Solomon- Head of DG SANTE, Medicines: policy, authorisation and monitoring*

*Michael Berntgen - Head of Product Development Scientific Support Department, EMA*

**10:10–12:45**    **Break-out sessions:**

1-    *Unmet medical need*

2-    *Incentives*

3-    *Medicines for children*

4-    *From R&D to patients*

5-    *Scientific developments*

**14:00-14:30**    **Debrief from break-out sessions**

**14:30-16:30**    **Open Space – Thinking Together**

*Discussion on topics coming directly from participants*

**16.30-16.45**    **Conclusions from Open Space**

*Chair: Prof Patrick Deboyser (European College of Parma)*

**16.45 – 17.00**    **Closing speech and next steps**

*Anne Bucher - Director-General DG SANTE*

## **Appendix 2: Specific questions for the breakouts**

### ***Unmet medical needs (Rapporteur: Kristina Larsson – EMA):***

- Unmet medical need: does it mean the same thing to everyone?
- Orphan condition: how can we support the development of medicinal products for patients still without treatment?
- Significant versus incremental benefit: how strictly should we follow the EU orphan legislation when applying this principle?

### ***Incentives (Rapporteur: Adriaan Brouwer - DG Competition)***

- Market exclusivity: how successfully has this incentive supported innovation? Has there been any unintended impact for availability and patient access?
- Reward for investment: how can we better guarantee that the reward is proportionate to the return on investment without knowing the cost of development?
- Other incentives: what other actions could be considered for areas without treatment?

### ***Medicines for children (Rapporteur: Dirk Mentzer - Chair PDCO)***

- How can we ensure an optimal support for the development of medicines for children without hampering research driven development of medicines for adults?
- Why are there so few paediatric medicines?
- EU orphan and paediatric legislation and the wider context: how well do the two regulations interact, including with other national and European policies?

### ***From R&D to patient (Rapporteur: Annika Nowak -DG RTD)***

The following questions were addressed:

- R&D: what are the main hurdles when developing orphan and paediatric medicinal products?
- Accessibility: how can public money for research be better invested in areas of unmet need? How can we make sure that medicines developed based on public funded research will reach patients across the EU?
- Real World Data/Real World Evidence: how will it influence the development, authorisation and access to new medicines?

### ***Scientific development (Rapporteur: Michael Berntgen - EMA)***

- What are the main scientific advances, which will influence future pharmaceutical product development? How will personalised medicine affect the landscape of orphan medicines and beyond?
- What does the innovation pipeline tell us and can the EU orphan and paediatric legislation accommodate these developments in a data driven society?
- How might scientific data and technological development affect the EU orphan and paediatric legislation?