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#### COVER NOTE

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From: Secretary-General of the European Commission,  
signed by Mr Jordi AYET PUIGARNAU, Director

date of receipt: 11 August 2020

To: Mr Jeppe TRANHOLM-MIKKELSEN, Secretary-General of the Council  
of the European Union

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No. Cion doc.: SWD(2020) 163 final

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Subject: COMMISSION STAFF WORKING DOCUMENT EVALUATION Joint  
evaluation of Regulation (EC) No 1901/2006 of the European  
Parliament and of the Council of 12 December 2006 on medicinal  
products for paediatric use and Regulation (EC) No 141/2000 of the  
European Parliament and of the Council of 16 December 1999 on  
orphan medicinal products

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Delegations will find attached document SWD(2020) 163 final, PART 2/6.

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Encl.: SWD(2020) 163 final, PART 2/6



Brussels, 11.8.2020  
SWD(2020) 163 final

PART 2/6

## COMMISSION STAFF WORKING DOCUMENT

### EVALUATION

**Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products**

{SEC(2020) 291 final} - {SWD(2020) 164 final}

## ANNEX 1: PROCEDURAL INFORMATION

### Lead DG, Decide Planning/CWP references

DG Health and Food Safety led the evaluation of the Orphan and Paediatric Regulations.

### Organisation and timing

The inter-service was set up in May 2015 to steer and provide input into the evaluation of the legal framework in the field of Orphan and Paediatric medicinal products. It included representatives from 6 Directorates General: Competition; Industry, Entrepreneurship and SMEs; Health and Food safety; Budget; Research and Innovation; Trade- and from the Legal Service and the Secretariat-General. The group met 11 times during the evaluation process (see Table A.1).

**Table A.1: Inter-Service Steering Group meetings**

| Dates            | Topics for discussion                                                                                                                             |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| 10 June 2015     | First meeting of the ISG on the 'Paediatric Report'                                                                                               |
| 3 November 2015  | Second meeting of the ISG on the 'Paediatric Report'                                                                                              |
| 20 May 2016      | Third meeting of the ISG on the 'Paediatric Report'                                                                                               |
| 8 March 2017     | Fourth meeting of the ISG on the 'Paediatric Report'                                                                                              |
| 16 April 2018    | Kick-off meeting for the "Study to support the evaluation of the EU Orphan Drug Regulation" between the Project Steering Group and the contractor |
| 2 July 2018      | Inception meeting on the study of the EU Orphan Drug Regulation                                                                                   |
| 22 November 2018 | Interim meeting for the "Study to support the evaluation of the EU Orphan Drug Regulation" between the Project Steering Group and the contractor  |
| 25 March 2019    | Inter-service Steering Group meeting to discuss the Draft Final Report of the "Study to support the evaluation of the EU Orphan Drug Regulation"  |
| 30 April 2019    | Inter-service Steering Group to discuss the Final Report of the "Study to support the evaluation of the EU Orphan Drug Regulation"                |
| 11 December 2019 | Discussion on the draft final staff working document.                                                                                             |
| 18 December 2019 | Discussion on the final staff working document.                                                                                                   |
| 27 March 2020    | Discussion on the revised final staff working document.                                                                                           |

### Consultation of the RSB (if applicable)

A meeting with the Regulatory Scrutiny Board took place on 12 February 2020.

Following the negative opinion issued by the RSB on 14 February 2020, the SWD has been revised to follow the recommendations from the RSB, namely:

- The report was shortened and restructured to focus on how these Regulations have contributed to today's situation for orphan and paediatric medicines.
- The intervention logic was simplified for clear linear dependency and the role of external factors was made more prominent.
- The description of the interventions explains now how the Regulations were expected to deliver. The analysis chapter elaborates on the changes to the policy context, which have taken place since the adoption of the Regulations, and their implications.

- More comparison to the US system is added throughout the document, together with the analysis of consistency measures done by the EMA.
- The cost-benefit for pharmaceutical industry was adjusted and concluded positive (Chapter 5.2 - Efficiency) by including a competitive profit margin of 10% to the benefit of the generic industry (thereby deviating from the outcomes of the contractor's study where this element was referred to as "normal profits", but not quantified, resulting de facto in profits being counted as costs).
- More analysis of availability and affordability of medicines across the EU is added together with the influencing role of external factors.
- The conclusions were redrafted to clarify main problems, their magnitudes and identify priorities for policy-makers' attention.

The revised SWD was resubmitted to the Board on May 12, 2020.

The RSB issued a positive opinion on 16 June 2020 with a few recommendations for improvement. Following the RSB advice given, the SWD has been revised, namely:

- Clarity was added throughout the report (case studies were included, for instance); language for non-experts was simplified, especially in the executive summary.
- Some sections were shortened and relevant information was moved to Annexes (especially from Chapter 5.2 to Annex 3).
- The improved clarity and shortening resulted in a SWD that has the same length in pages as the previous version.
- Additional information from the explanatory memorandum of the Orphan Regulation was added, with the aim to clarify what success was supposed to look like and help the reader judge the achieved results.
- A case study for an orphan paediatric medicine was added to illustrate inefficiencies of the system and a graphic description of the various pharmaceutical incentives was introduced to better illustrate the working of them.
- The role of external factors has been clarified in the intervention logic diagram.
- The conclusions provide clearer lessons learnt regarding the market-based approach of these Regulations.

### **External expertise**

The analysis of the evaluation is based on two independent studies conducted by Technopolis Group and Ecorys for the European Commission. They provided evidence-based answers to 16 evaluation questions, on which the analysis has been based in the light of the 5 Better Regulation criteria: relevance, effectiveness, efficiency, coherence and EU added value.

In addition to the above-mentioned studies the findings of the reports listed below have been carefully considered for the analysis in this staff working document:

Reports from the Commission to the European Parliament and the Council, on the 5 and 10 years of implementation of the Paediatric Regulation<sup>1</sup>

Reports from the EMA to the Commission on the experience acquitted as a result of the application of the Paediatric Regulation<sup>2</sup>

The parts relevant to the Paediatric and Orphan Regulations' incentives were also based on the findings of the study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe.<sup>3</sup>

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<sup>1</sup> Better Medicines for Children From Concept to Reality  
[https://ec.europa.eu/health/sites/health/files/files/paediatrics/2013\\_com443/paediatric\\_report-com%282013%29443\\_en.pdf](https://ec.europa.eu/health/sites/health/files/files/paediatrics/2013_com443/paediatric_report-com%282013%29443_en.pdf)

State of Paediatric Medicines in the EU 10 years of the EU Paediatric Regulation  
[https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/2017\\_childrensmedicines\\_report\\_en.pdf](https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/2017_childrensmedicines_report_en.pdf)

<sup>2</sup> General report on the experience acquired as a result of the application of the Paediatric Regulation (5-year Report to the European Commission, July 2012)  
[https://ec.europa.eu/health/sites/health/files/files/paediatrics/2012-09\\_pediatic\\_report-annex1-2\\_en.pdf](https://ec.europa.eu/health/sites/health/files/files/paediatrics/2012-09_pediatic_report-annex1-2_en.pdf)

General report on the experience acquired as a result of the application of the Paediatric Regulation (10-year Report to the European Commission, August 2017)  
[https://ec.europa.eu/health/sites/health/files/files/paediatrics/2016\\_pc\\_report\\_2017/ema\\_10\\_year\\_report\\_for\\_consultation.pdf](https://ec.europa.eu/health/sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf)

<sup>3</sup> Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018)  
[https://ec.europa.eu/health/sites/health/files/human-use/docs/pharmaceuticals\\_incentives\\_study\\_en.pdf](https://ec.europa.eu/health/sites/health/files/human-use/docs/pharmaceuticals_incentives_study_en.pdf)

## ANNEX 2: STAKEHOLDER CONSULTATION

### INTRODUCTION

This report provides an overview of the consultation activities carried out in the context of the joint evaluation of the EU Regulation on medicines for rare diseases and the Paediatric Medicines Regulation, the stakeholders that contributed and their opinions. In particular, stakeholder views have been gathered by means of several activities:

- Consultation activities carried out in the context of the study on the economic impact of the paediatric regulation;
- Open public consultation on the Paediatric Regulation;
- Feedback on the Roadmap for the evaluation on medicines for children and rare diseases (medicines for special populations);
- Workshop on “How to better apply the Paediatric Regulation to boost development of medicines for children”;
- Targeted and open public consultations in the context of the study to support the evaluation of the EU Orphan Regulation No 141/2000;
- Conference “Medicines for Rare Diseases and Children: Learning from the Past, Looking to the Future”.

The evaluation’s consultation strategy, aiming at reaching all concerned stakeholders’ groups, was firstly presented in the Roadmap.<sup>4</sup> As foreseen, both the 12-week public consultation and the targeted consultation involving Member States and specific groups took place. The stakeholders which contributed, as identified in the Roadmap, were the Member States (including national medicines’ regulators, payers and HTA bodies), the Agency, patients, industry and NGOs. Both qualitative and quantitative indicators were used to assess the input and to quantify the effect of the regulations’ provisions.

The objectives of each consultation activity are described in the sections below. An overview of the contributing stakeholders as well as a summary of the consultation results are also presented.

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<sup>4</sup> [https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-6059807\\_en](https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-6059807_en)

## **1. Consultation activities carried out in the context of the study on the economic impact of the paediatric regulation, including its rewards and incentives**

### **Objective**

The contractor carried out the study on the Economic impact of the Paediatric Regulation<sup>5</sup>, including its rewards and incentives, and also conducted an assessment of the costs and rewards of the Paediatric Regulation. This analysis was based on the results of a surveys of representative stakeholders.

### **Stakeholders**

A first survey was designed to PIP and waiver applicants, inquiring about the specific cost elements related to paediatric drug development. The relevant costs include all of the internal and outsourced costs that have been completed to date (administrative costs of a PIP / waiver application, R&D costs, excluding legal costs of SPC and manufacturing/distribution costs).

The survey additionally asked PIP applicants a set of open-ended questions about the relevance, effectiveness, efficiency, coherence and utility of the paediatric regulation. the replies received were followed up by phone interviews.

Details of the survey strategy are described in Annex A of the "Study on the economic impact of the paediatric regulation, including its rewards and incentives".

In addition to data collected via the survey to industry, the analysis was also built on a two-stage survey (Delphi) to expert stakeholders. The survey questionnaire was sent to stekeholders from across the EU, with 116 people ultimately completing the survey, although some respondents did not answer every question. Details of this survey are provided in Annex D of the economic study. The survey to expert stakeholders was developed based on an exploratory telephone consultations and pilots to uncover issues linked to social and broader economic impacts in the paediatric drug development value chain. The survey collected qualitative and quantitative estimates for the various dimensions of the impact as well as provided a set of open questions to identify further benefits of the Regulation and its impact.

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<sup>5</sup> [https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/paediatrics\\_10\\_years\\_economic\\_study.pdf](https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/paediatrics_10_years_economic_study.pdf)

## **Overview of results**

The data on costs and rewards have been used by the contractor for the cost benefit model in the study. The replies to the survey were divided into 5 main categories which correspond to the evaluation criteria: relevance, effectiveness, efficiency, coherence and EU added value.

The most important findings per criteria are presented in the following section.

### **RELEVANCE**

The objectives of the rewards provided by the Regulation are considered relevant or very relevant by most respondents. Some respondents note that the reward incentivised organisations to sponsor and support the development of paediatric medicines, including in rare/orphan disease. However, at the same time, respondents claimed that as a result of the necessary additional costs involved with submitting PIPs, individual organisations may not be able to achieve a positive return on investment.

### **EFFECTIVENESS**

The Regulation is considered effective in delivering on its objectives. Certain indicated that without the Regulation they would not have committed into paediatric medicines development. It was noted that the effectiveness is higher for high-volume products and lower for indications with very limited patient numbers. The complex and rigid regulatory system were instead indicated as main difficulties.

### **EFFICIENCY**

There is consensus amongst survey respondents that the 6-month extension to SPC is the most attractive reward provided by the Regulation. The SPC reward is seen as 'valuable' for the completion of an agreed PIP and the associated regulatory procedures, are seen as more efficient. However, the procedure towards an SPC reward is overly complex. The (long) time needed to conduct the necessary paediatric research and the and the limitations for requesting the SPC extensions are seen as problematics.

### **COHERENCE**

The assessment of coherence focuses on whether there are overlaps/complementarities between the rewards and related EU or Member State action. Most of the initiatives and benefits are complementary and there appears to be some overlap. Some EU Member States like the United Kingdom and France are providing national legislation to diminish the off-

label use of medicines for children, aimed at facilitating the development of paediatric medicines. In addition, in the area of paediatric (academic and hospital) research there are a number of large consortia which are involved in product development projects. Several organisations support this paediatric research by stimulating international cooperation and connecting existing networks.

## **EU ADDED VALUE**

In terms of the number of medicines that has become available, there is already a visible positive impact of the Paediatric Regulation. However, the impact of the regulation on research quantity and quality in children stemming from PIPs is not yet clear. Several measures could be taken to improve the effects of the Paediatric Regulation. Expanding funding options for research into paediatric medicines, e.g. via ‘Horizon 2020’ or other relevant EU Research funds (e.g. Innovative Medicine Initiative) might provide (also for companies) a framework for investment in paediatric research.

## **2. Public consultation on the Paediatric Regulation**

### **Objective**

On 15 November 2016, the Commission launched an open public consultation on the experience acquired from the application of the Paediatric Regulation.

This consultation was carried out to support the preparation by the Commission of a report on the experience acquired as a result of the application of Articles 36, 37 and 38 of the Regulation.<sup>6</sup> This included an analysis of the economic impact of its rewards and incentives, together with an analysis of the estimated consequences for public health of this Regulation, with a view to proposing any necessary amendments.

The Commission received 75 responses from a variety of stakeholders representing pharmaceutical undertakings, patient organisations, NGOs, as well as public institutions including regulatory agencies and national ministries. Healthcare professions, academia, research networks and other associations also contributed. The replies were qualitatively analysed per theme. There is an overall agreement in the replies by all categories of stakeholders. Specificities are provided below when necessary.

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<sup>6</sup> See Article 50(3) of the Paediatric Regulation.

First, the positive impact of the regulation was recognised with the majority of respondents agreeing that specific legislation is and will remain necessary to support the development of evidence-based medicines. At the same time, many respondents (in particular NGOs and patients associations) also mentioned weaknesses of the Regulation, e.g. concerning certain therapeutic areas such as paediatric oncology.

As far as the paediatric needs are concerned, it was recognised that over the last ten years, some therapeutic areas have seen important progress, while in others changes did not materialise (yet). Some respondents also alluded to the challenge to define and agree on paediatric needs, if this is understood as prioritising one therapeutic area over another.

Concerning the availability of paediatric medicines in the EU, some respondents pointed out that authorisation does not automatically equate with availability, while others referred to cost factors or prescription habits of physicians.

Concerning the average costs per paediatric investigation plan, some of the respondents noted the relatively small averages compared to the overall very large sums spent on drug development, while others criticized the use of averages, as potentially misleading in view of the variability of development costs. With regards to the reward system, many considered that in general it functions well, while some pointed to inefficiencies or questioned whether it is sufficient across all therapeutic areas. Concerning the orphan reward, respondents generally supported the separate orphan reward, highlighting its effect for products that are not protected by a patent. At the same time, many industry respondents considered the option to withdraw the orphan status in order to benefit rather from the SPC reward as a legitimate option to choose the most appropriate reward.

Many respondents also agreed on the disappointing uptake of the PUMA concept, with one of the main reasons often being the lack of sufficient incentives to promote the research in off patent paediatric indications, especially pricing pressure for established compounds. On the question whether PUMA should be maintained, some argued that despite the small number of authorised products, it might still prove beneficial to have such a specific marketing authorisation, while others took the view that the concept could be shelved, especially in case alternative methods would be developed to financially support paediatric research into off-patent medicines.

The question on waivers and the ‘mechanism of action’ principle was one of the most debated issues within the consultation. Many respondents (mostly patients organisations, research associations and NGOs) referred to paediatric oncology as an example where mechanism of action based Paediatric Investigation Plan (PIP) could help to better guide drug development. At the same time, some respondents referred to the need to find a fair balance

between possibilities to address unmet paediatric needs and the need to ensure a clear and predictable scope of a PIP.

The positive effect of the Paediatric Regulation on paediatric research within the EU was widely recognised by all categories of stakeholders. This also led to a broad increase of available expertise and collaboration between relevant actors, including networks. At the same time, some respondents referred to areas of improvement, particularly with regard to infrastructure support.

**A report summarising the stakeholders' replies to the OPC was published on the Commission website and can be found at: [https://ec.europa.eu/health/sites/health/files/files/paediatrics/2016\\_pc\\_report\\_2017/2016\\_pc\\_report\\_2017\\_summary.pdf](https://ec.europa.eu/health/sites/health/files/files/paediatrics/2016_pc_report_2017/2016_pc_report_2017_summary.pdf)**

### **3. Feedback on the Roadmap on the Evaluation of the orphan and paediatric legislation**

#### **Objective**

From 11 December 2017 until 8 January 2018, stakeholders had the opportunity to provide their feedback on the roadmap for the evaluation of the Orphan and Paediatric legislation.

#### **Stakeholders and overview of results**

In total 23 replies were received: 4 from business associations, 2 from companies, 2 from public authorities, 5 from NGOs, 3 from academic/research institutions, 5 from EU citizens and 2 from non-EU citizens.

Responses were not divided per evaluation criteria. Any response that differed from the average was included into the summary of responses.

The majority of the replies welcomed the evaluation of the two legislations in order to further explore their effectiveness over the years. However, one stakeholder clearly asked for maintaining the current regulatory framework without any change and supported a more pragmatic implementation. By contrast, one stakeholder openly encouraged the reform of the legislation on the rewards.

In particular, with regards to the orphan reward many industry respondents considered the option to withdraw the orphan status in order to benefit rather from the SPC reward as a legitimate option to choose the most appropriate reward. In addition, on deferrals, it was

noted that many companies still perform adult studies first, which often makes deferrals unavoidable. This may change over time, once newer development models become state of the art. Some respondents also highlighted that from a company perspective long deferrals should not necessarily be seen as an advantage, as they may compromise the possibility to obtain the reward.

Three replies urged the Commission to consider the differences between the objectives of the two legislations. Six correspondents asked for more clarifications regarding the evaluation, either concerning the scope of the study either on the methodology that would be used. Also, stakeholders asked for more explanations on the objective behind this evaluation. One reply asked clearly for an impact assessment analysis in order to evaluate the potential consequences of the evaluation. Pricing and reimbursement came up twice as a very important factor which should be further explored and requires more transparency from the industry and the Member States. One stakeholder asked to explore ways to reduce the bureaucratic burden of clinical trials in order to allow for more research in the EU territory.

The Commission was also urged to consider how both Regulations could better incentivise science-driven paediatric development plans based on the disease's biology and the drug's mechanism of action. For example, one stakeholder urged Commission to introduce 'mechanism of action principle' into the Paediatric Regulation.

Finally, clarifications were asked on the link between the Technopolis study on the Paediatric Regulation and the Technopolis study on the Orphan Regulation.

**The full set of contributions received are published on the Commission website and can be found here: [https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-6059807/feedback\\_en?p\\_id=146293](https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-6059807/feedback_en?p_id=146293).**

#### **4. Multi-stakeholder workshop on “How to better apply the Paediatric Regulation to boost development of medicines for children”**

##### **Objective**

On 20 March 2018, the European Commission and the Agency convened a multi-stakeholder workshop to discuss and identify ways to improve the implementation of the Paediatric Regulation.

##### **Stakeholders & overview of results**

The workshop brought together around 160 participants from different groups; patients and carers, academics, healthcare professionals, and pharmaceutical industry representatives as

well as clinical trial assessors from national competent authorities (NCAs), ethics committees, the Agency including representatives of the Paediatric Committee (PDCO) and the European Commission.

The various suggestions that were brought up during the workshop can be summarised around four main areas. Firstly, it was recognised that there is a need to properly assess disease burden, including the relevance of a condition in the paediatric population, its seriousness, and the availability and suitability of treatments. Central to the discussion was the understanding that multi-stakeholder engagement is key and that a patient-centred approach (rather than drug-centred approach) is needed. It was also deemed important to build on experience with successful models such as the Accelerate Platform<sup>3</sup> in the area of paediatric oncology.

Secondly, the properties of a given medicinal product, including its mode of action and pharmacological characteristics in various age groups should be taken into account, alongside other considerations such as whether the treatment is potentially curative or disease-modifying, whether it will impact disease progression or mainly target disease symptoms and its impact on quality of life. Patient representatives, industry and other stakeholders also noted that consideration should be given to whether or not there are other available treatments including non-pharmacological interventions.

Thirdly, several participants insisted on the need to share information and data from research in a transparent fashion and to make it publicly available; such transparency would provide insight on the pipeline of new developments, assist with the design of future trials and help avoid the conduct of unnecessary trials. It was emphasised that standardised terminologies and study methodologies are important in order to permit data merging and avoid fragmentation of data. The importance of registries, like Orphanet,<sup>7</sup> was highlighted, alongside with the timely completion of the PIPs and the better handling of PIP applications.

Finally, participants agreed that a global perspective in identifying paediatric medical needs and determining regulatory requirements is very important.

**A report was published on 30 May 2018 on the website of the European Medicines Agency and can be found at: [https://www.ema.europa.eu/en/documents/report/how-better-apply-paediatric-legislation-boost-development-medicines-children-report-multi\\_en.pdf](https://www.ema.europa.eu/en/documents/report/how-better-apply-paediatric-legislation-boost-development-medicines-children-report-multi_en.pdf)**

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<sup>7</sup> <https://www.orpha.net/consor/cgi-bin/index.php>

## 5. Consultation activities carried out in the context of the study to support the evaluation of the EU Orphan Regulation No 141/2000

### Objective

In order to gather stakeholders' views to feed into the evaluation of the EU Orphan Regulation, an **online public consultation (OPC)** and several **targeted consultations** were organised with the help of an external contractor. The open public consultation took place between October 2018 and January 2019 via the online platform of the European Commission. The targeted consultations took place between August 2018 and January 2019. They consisted of interviews and online surveys. In response to the targeted surveys additional supporting documentation was received. Also written ad hoc contributions were provided.

The consultation activities aimed to retrieve information mainly on:

- Experiences with and evidence on relevance, effectiveness, efficiency, coherence and EU added value of the EU Orphan Regulation
- Experiences with and evidence on efficiency of the Agency's procedures pertaining to the implementation of the EU Orphan Regulation
- Experiences with and evidence on issues that affect access to orphan medicines in Europe, both in general and in direct relation to the EU Orphan Regulation
- Experiences regarding the interplay between the Orphan and Paediatric Regulations.

### Stakeholders

The stakeholders identified and the consulting strategy, as decided together with the evaluation's Project Steering Group of the Commission, are presented in the table below:

**Table A.2: Stakeholder groups and consultation methods**

| <b>Stakeholder group</b>                                                                                | <b>Consultation method</b>     |
|---------------------------------------------------------------------------------------------------------|--------------------------------|
| <b>Patients living with rare diseases and carers</b>                                                    | Online public consultation     |
| <b>Health professionals</b>                                                                             | Online public consultation     |
| <b>National public authorities (e.g. ministries of health, public health authorities, HTA agencies)</b> | Interviews, targeted survey V1 |
| <b>Developers of innovative medicines</b>                                                               | Interviews, targeted survey V2 |
| <b>Developers of generic / biosimilar medicines</b>                                                     | Interviews, targeted survey V3 |
| <b>Patient and consumer organisations</b>                                                               | Interviews, targeted           |

|                                       |                                |
|---------------------------------------|--------------------------------|
|                                       | survey V4                      |
| <b>Academic researchers / experts</b> | Interviews, targeted survey V5 |

To adequately cover the required scope of the study, it was decided to develop and distribute 5 separate versions of the **targeted surveys**. These respectively aimed at: 1) representatives of national public authorities in EU Member States, 2) sponsors of orphan medicinal products, 3) developers of generic medicines for rare diseases, 4) patient and consumer organisations, and 5) academic researchers and experts.

### **Online public consultation<sup>8</sup>**

The online public consultation was conducted via a survey consisting of open and closed questions about knowledge of and experiences with orphan medicines, policy challenges, experiences with the EU Orphan Regulation, and the availability, affordability and accessibility of orphan medicines, both in general and at member State level. A total of 145 responses was received.

### **Targeted surveys**

A total of 155 responses were received and then further divided in 5 groups: national public authorities, developers of innovative (orphan) medicines, developers of generic medicines, academic researchers/experts and patient and consumer organisations.

In total, 19 EU Member States are represented individually in the survey. Among ‘other’ respondents, 2 represented non-EU Member States (Iceland, Norway) and 2 were from organisations with activities in multiple EU countries.

### **Interviews**

In total, 36 separate interviews were completed. Representatives of the US Food and Drug Administration and of the Pharmaceuticals and Medical Devices Agency in Japan were also interviewed to obtain information necessary for a comparison to the regulatory frameworks for orphan medicines in these two jurisdictions.

### **Ad hoc contributions**

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<sup>8</sup> The replies are publicly available at: [https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-6059807/public-consultation\\_en#consultation-outcome](https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-6059807/public-consultation_en#consultation-outcome)

Unsolicited written commentary was received from the Heads of Medicines Agencies Permanent Secretariat (HMA), the European Consumer Organisation (BEUC), and the German Pharmaceutical Industry Association (BPI).

Study findings were presented for discussion and validation at two separate meetings: on 21 February 2019 during a meeting of the Agency's Committee on Orphan Medicinal Products (COMP) and on 1 April 2019 at a meeting of the Pharmaceutical Committee with national representatives of Member States. During these meetings, oral comments from participants were collected which were fed into the analysis

### **Overview of results**

The replies to both surveys were divided into 5 main categories which correspond to the evaluation criteria: relevance, effectiveness, efficiency, coherence and EU added value. These views have been taken into account when drafting the evaluation SWD.

The most important replies per criteria are presented in the following section.

## **RELEVANCE**

### **Necessity for an EU Orphan Regulation**

Most contributors agreed or strongly agreed that, prior to 2000, there was a need for concerted EU action to stimulate the development of orphan medicines and promote access to such products. However, there were differences on whether this support should include financial support in the form of a time-limited marketed exclusivity.

### **Availability of and access to orphan medicines in EU Member States**

Representatives of national public authorities, patient and consumer organisations, and academic experts all were asked via survey to what extent orphan medicinal products are placed on their national markets directly by marketing authorisation holders. Those with sufficient information to estimate this, mostly suggest national availability falls above 50% or even 75% of all orphan medicines, though in some countries it was reported as below 25%.

Only around half of all respondents felt able to estimate how long it takes, on average, for orphan medicines to reach their national markets after marketing authorisation.

## **EFFECTIVENESS**

## **Role of incentives in promoting development of orphan medicines**

Developers were asked about the general importance of the incentives offered by the EU Orphan Regulation, such as the Agency's fee reductions, the aid for research<sup>9</sup>, waivers or the 10-year period of market exclusivity of an orphan product. Survey correspondents deemed all incentives important or highly important, but most had no experience with the 'aid for research' incentive. Interviewees also emphasised the importance of the full set of incentives, remarking on how they work together to create conditions conducive to product development.

### **EFFICIENCY**

Strong concerns were expressed by nearly all these stakeholders about the very high prices of some orphan medicines, with expectations of this further increasing, but with frequently limited evidence of effectiveness. It was furthermore noted by several such stakeholders that the balance with the size of the 'reward' is almost impossible to assess as they observe a lack of transparency from industry in disclosing R&D costs for development of (orphan) medicines.

### **COHERENCE**

#### **Coherence and complementarity with other EU interventions**

The majority of representatives of national public authorities agreed or strongly agreed that the EU Orphan Regulation is coherent with other EU policies and actions to support development of pharmaceutical products. Most academic researchers were unable to comment on this.

### **EU ADDED VALUE**

Representatives of national public authorities in Member States indicated that the added value brought by the EU Orphan Regulation resides foremost in the offer of an additional set of incentives. **Error! Reference source not found.** Both in comments to the survey and in interviews, some stakeholders expressed that the EU Orphan Regulation has contributed to structuring the national expertise in rare diseases and helped to promote national rare disease plans.

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<sup>9</sup> Aid for research incentive is the possibility for Member States or other programmes to offer research grants or other forms of support to developers of designated orphan medicines.

## **6. Conference on "Medicines for Rare Diseases and Children: Learning from the Past, Looking to the Future"**

### **Objective**

The conference entitled "Medicines for Rare Diseases and Children: Learning from the Past, Looking to the Future" which took place on 17 June in Brussels aimed at bringing together stakeholders from different groups for an active discussion based on the preliminary findings of the ongoing study to support the evaluation of the EU Orphan and Paediatric Regulations. The conference 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.

Five break-out sessions were organised, during which the following topics were addressed: unmet medical needs, incentives, medicines for children, from R&D to patients and scientific developments.

### **Stakeholders & overview of results**

The results were assessed qualitatively per theme; the most important conclusions of each break-out session are presented below.

### **Unmet medical needs**

The EU Regulation on conditional marketing authorisation provides a definition of unmet medical needs. However, participants questioned whether it is understood in the same way by all involved parties. The value of input from 'expert patients' concerning how unmet medical need is exactly defined as well as the quantification of unmet medical need was therefore recognised. It was also remarked that a broader understanding of unmet medical need could serve both paediatric and orphan medicines development. In addition, orphan designation 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.

Various groups of stakeholders reflected on the interplay between the EU Orphan Regulation and the Paediatric Regulation. In particular, they expressed their concerns on the definition of a condition under the EU Orphan Regulation framework and the granting of PIP waivers, which were thought to negatively impact the development of treatments for children with rare diseases, including cancer.

## **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 a medicine's development cost may not always be clear. It would be important for any financial reward scheme to incorporate the entire life cycle of a product.

## **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 medicines development for children, both in terms of physiology and the development process itself. 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.

## **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. An early dialogue between all players involved was suggested, among others, as a possible way to address these hurdles.

## **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 relevant views expressed by the stakeholders were taken into consideration when drafting this evaluation.

**A detailed report was published on the Commission website and can be found at: [https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/ev\\_20190617\\_report\\_en.pdf](https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/ev_20190617_report_en.pdf)**

## CONCLUSIONS

The consultation activities provided a wide range of opinions and experience concerning the implementation of the two regulations in terms of what has worked well so far and what has not worked so well, as seen through the eyes of the stakeholders consulted. This information is widely used in the evaluation to complement and triangulate the information obtained from other sources.

The two physical meetings (workshop and conference) with EU stakeholders provided a valuable opportunity to promote their engagement in the evaluation while offering an additional occasion to provide feedback, thus increasing the chances of collecting more complete and representative responses.

The feedback on the roadmap allowed the stakeholders to express concerns and their opinions on the process and the overall exercise of the evaluation. This information has been used by the Commission services during the study on the orphan regulation.