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European Commission

INCEPTION IMPACT ASSESSMENT

Inception Impact Assessments aim to inform citizens and stakeholders about the Commission's plans in order to allow them to provide feedback on the intended initiative and to participate effectively in future consultation activities. Citizens and stakeholders are in particular invited to provide views on the Commission's understanding of the problem and possible solutions and to make available any relevant information that they may have, including on possible impacts of the different options.

TITLE OF THE INITIATIVE	Revision of the EU legislation on medicines for children and rare diseases
LEAD DG (RESPONSIBLE UNIT)	SANTE (Unit B5: Medicines: policy, authorisation and monitoring)
LIKELY TYPE OF INITIATIVE	Legislative proposal of the European Parliament and of the Council
INDICATIVE PLANNING	Q1 2022
ADDITIONAL INFORMATION	Evaluation of the legislation for medicines for rare diseases and children

The Inception Impact Assessment is provided for information purposes only. It does not prejudge the final decision of the Commission on whether this initiative will be pursued or on its final content. All elements of the initiative described by the Inception impact assessment, including its timing, are subject to change.

A. Context, Problem definition and Subsidiarity Check

Context

The Regulation for medicines for rare diseases and the Regulation for medicines for children were adopted in 2001 and 2006 respectively, to improve treatment options of 30 million European patients affected by one of the over 6000 rare diseases and of over 100 million European children. At the time, limited or no medicinal products were available for both groups. This was because the market size was generally small and the research and development of products, including the conduct of clinical trials, was more complex. Both Regulations have introduced a mixture of obligations, incentives and rewards to address the apparent market failure. The objectives of the two Regulations partly overlap, as many diseases that affect only children are rare and rare diseases often also affect children.

In 2016, the Council called on the Commission to examine the impact of pharmaceutical incentives on the availability and accessibility of medicines for rare diseases. The European Parliament issued a resolution on EU options for improving access to medicines, mentioning also the issue of access to medicines, for children and for rare diseases. In its 2016 Resolution, the Parliament recognised that the Paediatric Regulation has been beneficial to children overall (but not sufficiently effective in certain therapeutic areas - notably paediatric oncology and neonatology). It therefore called on the Commission to consider revising the Regulation. The revision of the two legislations is also one of the actions of the EU Pharmaceutical Strategy.

The joint evaluation of the two Regulations has shown that both legislative instruments have stimulated research and development of medicines to treat rare diseases and of medicines for children.

However, it also showed shortcomings in the functioning of the existing legal framework. This is partly due to the legislation not being able to stimulate development of medicines in areas of unmet needs (e.g. 95% of rare diseases still have no treatment option) and to better ensure that European patients actually get the medicine (*access*), independently from which country they live. Moreover, weaknesses relate to the Regulations not being flexible enough to allow scientific developments and certain procedures turned out to be inefficient and burdensome.

Possible solutions to these shortcomings and better synergies between the provisions of the two Regulations will

be analysed in an Impact Assessment.

The Regulations for medicines for rare diseases and children provide incentives and rewards, and their design can influence business decisions about research and development for new medicines as well as whether such investments can be focused in areas of unmet need. In addition, the system of incentives can impact market competition aspects and therefore (indirectly) influence availability of and access to medicines as well as raise concerns over health systems' budgetary sustainability. These elements will be assessed in the options for revision of the Regulations in the impact assessment.

However, the two Regulations cannot be seen in isolation as their success is also linked to areas were Member States have (near) exclusive competence (e.g. pricing and reimbursement of medicines, corporate taxation, and healthcare organisation) and to strategic decisions by companies. The evaluation showed that these external factors have gained importance and influence over time, particularly for rare diseases.

The revision of both Regulations will take these external factors into account when assessing options for solutions. These factors will be further addressed through other actions within the EU Pharmaceutical Strategy. Furthermore, the medicines development is global and any modification to the current system will need to be benchmarked with other jurisdictions.

The interplay with the Supplementary Protection Certificate ("SPC") is a factor affecting the efficiency of the Regulation on medicines for children. The SPC legislation is currently undergoing an evaluation.[1] Possible changes in the SPC system may address some of the inefficiencies identified in the evaluation of the Regulation for medicines for children.

The COVID-19 pandemic may affect the development and accessibility of medicines for rare diseases and for children. For example, while it has been possible to speed-up agreement for the performance of clinical studies with children for some COVID-19 related medicines, the effect of the pandemic on the actual conduct of such studies still has to be verified.

Problem the initiative aims to tackle

The main problems indicated in the evaluation of the legislation for medicines for rare diseases and children are:

1. **Insufficient development in areas of greatest unmet medical needs for patients:** the development of medicines is not covering all major therapeutic areas. In the area of medicines for rare diseases, the evaluation found that 95% of rare diseases still have no treatment option. Concerning medicines for children, developments do not address sufficiently the highest unmet needs of children (areas like mental and behavioural disorders and neonatology, for instance). Furthermore, both Regulations have been built around "one-size-fits all" incentives and rewards, which do not always provide an adequate tool to stimulate developments in areas of unmet needs. For example, the 6-month SPC extension that can be granted after the completion of paediatric clinical studies has not incentivised research and development in diseases that affect only children or in areas where the unmet therapeutic needs for children are bigger.

2. **Availability and accessibility varies considerably across Member States:** the evaluation has shown that the medicines developed thanks to the two Regulations, once authorised are not *accessible* to patients equally in all Member States. In some Member States, market entry is delayed or not happening at all. Currently, there is no link in the Regulation for medicines for rare diseases between the provision of incentives and the placing on the market in most/all Member States. Furthermore, generic competition after the expiry of exclusivity periods does not happen or happens only with delay, which also affects access. Finally, the lack of generic/biosimilar competition raises questions on the long-term budgetary sustainability of health systems, which in turn is expected to impact on the availability and accessibility of healthcare across the board in specific Member States.

3. **Scientific and technological developments cannot be fully exploited:** current legal definitions, used in both Regulations, are directly linked to the concept of a disease. They are not always adequate to cater for advances in science, such as the use of biomarkers in medicines' discovery, advanced therapies, or the use of innovative clinical trials designs. Therefore, these advancements in science cannot always be

[1] The SPC is an intellectual property right that serves as an extension to a patent right and is applicable to innovative medicinal products.

used to the benefit of children and patients with rare diseases. Scientific developments, such as personalised medicine approaches and the use of biomarkers, may hold great potential for optimal tailoring of treatments to diseases, but they should not lead to unnecessary multiplication of rare diseases out of common diseases. The designation criteria set in the Regulation may have been used to split common diseases into many subsets, which may be 'artificially' considered as 'rare' diseases (i.e. certain forms of common cancers) and hence have led to the multiplication of exclusivity periods in areas where there is no market failure. Finally, the provisions on medicines for children may exclude from the obligation to conduct clinical studies in children certain medicines developed for adults and which, in view of their mechanism of action, may be promising for the treatment of certain diseases in children, which are unrelated to the original adult disease. This is often the case for anti-cancer medicines.

4. **Certain procedures are inefficient and burdensome:** there may be room for simplification and streamlining of procedures and internal processes including within the European Medicines Agency ('Agency') to avoid the risk of possible inconsistencies and delays. Furthermore, some reporting requirements create administrative burden without fully achieving their objective (e.g. the obligation for sponsors to submit an annual report on the orphan designation to the Agency). Moreover, the extension of the SPC requires individual requests to each national patent office, making the procedure for obtaining this reward complex and time-consuming and results often in unreliable outcomes.

Without an intervention, these problems will continue to persist and may even grow (new scientific and technological developments will continue and may accelerate, for instance).

Basis for EU intervention (legal basis and subsidiarity check)

Legislation regulating medicinal products is nowadays based on Articles 114(1) and 168(4)(c) of the Treaty on the Functioning of the European Union (TFEU). EU action to ensure the development of medicines for rare diseases and for children allows for medicines successfully developed to take advantage of the whole EU market. Moreover, uncoordinated measures by the Member States in this area may result in distortions of competition and barriers to intra-Union trade. By boosting medicines' research and development, the legislation also aims to improve the competiveness of the EU industry.

As a shared competence with the Member States, and in line with the principle of subsidiarity, the Treaty also gives the EU a mandate to set out measures establishing high standards of quality and safety for medicinal products.

The authorisation of medicinal products, including orphan and paediatric medicines, is fully harmonised at EU level. Thus, Member States cannot introduce specific provisions at national level in this field. Nevertheless, national pricing & reimbursement decisions does in fact determine whether a patient actually *gets* a medicine.

B. Objectives and Policy options [

Objectives for revision of the two Regulations

- To foster research and development of medicines for rare diseases and for children, especially in areas of unmet need and in better alignment with patient needs;
- To contribute to ensuring the availability and timely access of patients to orphan and paediatric medicines;
- To ensure that the legislation is fit to embrace technological and scientific advances;
- To provide effective and efficient procedures, for assessment and authorisation of orphan and paediatric medicinal products.

Baseline

Medicines for children:

The current Regulation will continue to apply. Concerning the development of medicinal products in areas of pressing unmet needs for children, non-legislative measures have not achieved major progress. Therefore, no major advances are to be expected in the future without an EU intervention. Non-legislative actions developed in the framework of the joint EMA - European Commission Paediatric Action Plan may allow for limited adaptation to technological and scientific advances.

The instruments of the legislation to ensure access and availability of medicines for children in the whole EU are limited. The launch of a paediatric indication or product on a national market is often linked to the launch of the corresponding adult product. It has been observed that companies often rely on a staggered roll-out of new products, resulting in delays until the product is finally available throughout the EU.

The possibility for simplification of regulatory procedures is limited and would be based on guidelines. Reduction of the administrative burden linked to the SPC extension reward would depend on a possible legislative follow up to the evaluation of the SPC Regulation.

Medicines for rare diseases:

The current Regulation will continue to apply. No major improvements may be expected in addressing the gaps in the development of medicinal products for rare diseases in areas of pressing unmet needs (i.e. ultra-rare diseases). Furthermore, *accessibility* to these products will remain an issue for many patients across the EU, as there are currently no obligations for companies to place authorised medicines on the market in all Member States.

Regular updates of various guidelines for the development and assessment of medicines for rare diseases may provide limited improvements in adaptation to some scientific advances.

However, these updates will not be able to address the problems and shortcomings presented in Section A of this document. For example, on the one hand the designation criteria would not be flexible enough to allow for scientific developments. On the other hand, they would allow artificial splitting of common diseases into rare subsets.

Options

The impact assessment will consider commonalities and possible combinations of the options. A coherent approach will be ensured when proposing and comparing options, taking into account possible synergies, overlaps and potential common solutions for both areas of rare and children's diseases.

Medicines for children

All options (as mentioned below) will build around a series of common elements. In particular:

- Unmet medical needs of children will be better identified. This would help focusing research and development efforts *in areas where children do not have treatment options*. For example:
    - Criteria to determine unmet needs for children and a system to identify products developed to address such needs would be set up in the legislation.
    - Products identified by the system mentioned above would be eligible of priority assessment and increased scientific support by EMA. A system similar to the existing PRIME scheme could be put in place.
    - Dedicated research funding for academia and SME to support developments in such areas of unmet needs for children will also be considered.
- To address issues related to *availability and access* to medicines, improved rules linking the rewards with the placing on the market of the products in most/all Member States will be explored.
- To tackle current *inefficiencies*, while also better catering for *scientific and technological developments,* when necessary, procedures to determine which clinical studies should be conducted in children for each new medicine under development, will be streamlined and made more flexible and adapted to the innovative ways medicines are developed. This could also include:
    - A revision of the conditions for granting exemptions from the obligation to study all new medicines in children. This would ensure that products that could be beneficial for children due to their mechanism of action, for diseases different from those in adults (as it is the often the case for cancer in children), are effectively tested for them.
    - Limitations/conditions to the delays allowed for the conduct of clinical studies in children.

Besides these elements, modifications to the current system of rewards will be considered in **four different options**. The changes related to the rewards aim to tackle the problems linked to the *unmet medical needs* and *unequal access* to medicines for children.

Option 1

The 6-months SPC extension will remain the main reward provided by the legislation. The possibility to link this reward to a timely completion of a Paediatric Investigation Plan (PIP) as well as to the placing on the market in most/all Member States will be assessed. This would aim at fostering the placing on the market of new medicines for children in most/all Member States.

The utility of the other rewards provided by the Regulation will also be assessed. This especially concerns the

extension by 2 years of the market exclusivity for medicines for rare diseases for children. Ways to improve the functioning of the existing scheme intended to boost the development of possible new uses in children from old and off-patent products ("PUMA" scheme) will be explored.

Option 2

This option builds on Option 1, but would limit the 6-months extension of the SPC only to medicines addressing unmet needs for children. This would selectively boost medicines development in such areas and be similar to the US system.

This option would reduce the number of medicines that would benefit from a reward. In turn, it would allow earlier generic entry on the market for products not fulfilling an unmet medical need for children, thereby increasing their accessibility.

Option 3

This option builds on Options 1 with the 6 months SPC extension as the main reward for the completion of a PIP. For products addressing unmet needs for children, a novel reward would complement or replace the SPC extension. Possible novel rewards could involve the extensions of regulatory rewards (data and market protection) or various types of transferable "vouchers" (e.g., priority review or regulatory rewards vouchers).

The impact of such novel rewards on the availability, timely patient access and competition as well as health systems' budgets will also be assessed, including conditions and limitations.

Option 4

This option builds on Options 2 and 3. No extension of the SPC would be granted. Instead, a novel reward as described in Option 3 would be granted to medicines addressing unmet needs for children in order to selectively boost medicines development in such areas.

This option would reduce the number of medicines that would benefit from a reward, In turn, it would allow earlier generic entry on the market for products not fulfilling an unmet medical need for children, thereby increasing their accessibility.

Medicines for rare diseases

All options (as mentioned below) will build around a series of common elements. In particular:

- To foster *development in areas of greatest unmet medical needs* in rare diseases:
    - Criteria to determine unmet needs for patients suffering from rare diseases would be set up in the legislation and a system to identify products developed to address such needs.
    - Enhanced regulatory support should be introduced: products developed to address an unmet medical need in rare diseases would be eligible to priority assessment and increased scientific support by the Agency (like the existing PRIME scheme). Dedicated research funding for academia and SMEs will be available to support developments in areas of unmet needs in rare diseases.
    - Account should be taken of the jurisprudence of the EU courts with regard to the designation criteria for orphan medicinal products and integrate learnings to ensure that new products provide a real benefit to patients and the therapeutic landscape.
- To improve *availability and accessibility* across Member States:
    - Faster generic/biosimilar competition should be fostered, e.g. by ensuring that generics/biosimilars can enter the market at day-1 of the expiry of the exclusivity period;
    - Companies that lose the commercial interest in a product should be encouraged to offer it for transfer to another company rather than withdrawing it, thereby guaranteeing market continuity.
    - A temporal validity of a designation should be introduced to encourage timely product development (an adequate time limit will be explored in the impact assessment phase).
    - Cumulative numbers of people affected by all rare conditions targeted by the same orphan medicine should be calculated in order to avoid overcompensation and blocking the entry of generics/biosimilars.
- To allow for *scientific developments,* the criteria for designation should be more flexible. Current legal definitions are directly linked to the concept of a disease. These legal provisions require amendment to ensure that the Regulations accommodate new scientific developments. Nevertheless, to avoid that the provisions of the regulatory framework could be used in a way leading to unnecessary multiplications of

rare diseases out of common diseases, it will not be possible to obtain orphan designation for subsets of common diseases.

- To make certain *procedures more efficient and less burdensome:*
    - The 'insufficient return on investment' criterion should be discarded as it has never been used (difficult to predict and calculate);
    - Ensure better coordination between scientific committees at the Agency and a faster assessment of the marketing authorisation applications. This may include transferring the responsibility for identifying medicines for use against a rare disease ('orphan designation') from the Commission to the Agency.

Besides these elements, modifications to the current system of designation criteria for orphan medicinal products and incentives will be considered in **four different options**. These changes aim to tackle the problems linked to *unmet medical needs, unequal access* to medicines for rare diseases and *technological and scientific advances* not being fully exploited.

Option 1

The criterion for granting an orphan designation to a medicine under development will remain the number of people affected (current threshold of 5 in 10 000).

The market exclusivity will remain the main incentive provided (but its duration will be variable). The length would depend on the type of development (innovative products; re-purposed products; second/multiple indications). We will investigate different criteria under which companies can ask for extension of the market exclusivity (e.g. insufficient return on investment, availability of the product in all/most Member States). Its maximum length, including extensions, will remain 10 years and it may be set aside under certain conditions (insufficient supply, consent or the provision of a better product).

Option 2

This option builds on Option 1. However, it proposes changes to the current criteria for designation in order to better identify rare diseases. We will propose changes to the current threshold of total number of cases of a disease at a specific time. In parallel, we will also explore if a *different* criterion could be used to identify specific rare diseases (e.g. rare cancers) by measuring the number of people that acquired the disease during a specified time-period (incidence). Different criteria would apply depending on the type of the disease.

Option 3

As regards the criteria for designation and incentives, this option builds on Option 2 and will consider an *alternative* incentive. Market exclusivity as per Option 2 will remain the standard incentive provided to medicines for rare diseases. For products addressing an **unmet need in rare diseases** and rare paediatric diseases**,** we will explore **novel incentives** that complement or replace the market exclusivity. Examples of possible novel incentives are detailed under Option 3 of medicines for children.

The impact of such novel rewards on the availability, timely patient access and competition as well as health systems' budgets will also be assessed, including conditions and limitations.

Option 4

This option builds on Option 3 for criteria for orphan designation incentives. Market exclusivity will no longer be an incentive provided for all medicines for rare diseases. However, for products addressing an **unmet need in rare diseases and rare paediatric diseases,** market exclusivity or novel incentives will be explored as main reward.

The various options presented aim at addressing the problems identified in a proportionate way, limiting the European action to a minimum as well as financial or administrative cost for the Union, national governments, regional or local authorities, economic operators or citizens. A proportionality assessment of the various options will be conducted in the impact assessment.

C. Preliminary Assessment of Expected Impacts

Likely economic impacts

The initiative is expected to decrease the overall financial burden related to the provision of medicines for rare

diseases and children on **national health systems**/budgets. At the same time, it will be assessed whether additional costs to national health systems may derive from possible extensions of regulatory protection periods. This could be due, for instance, to possible delays in the placing of generic/biosimilar medicines on the EU market.

For **pharmaceutical industry**, on the one side the options leading to a reduction of the current rewards and incentives (Options 1 and 4 for orphans and Options 2 and 4 for paediatrics) could lead to a reduced financial compensation. On the other side, the introduction of novel incentives and rewards (Options 3 & 4) is intended to compensate development in specific areas of unmet medical need. The possibility to adapt the areas where such novel incentives and rewards would be applicable is meant to avoid possible distortions in the systems and possible overcompensations and to focus on the right unmet medical need.

A revised system of incentives may on the one hand boost research and innovation in new therapeutic areas in line with scientific progress. On the other hand, a variable duration of the market exclusivity for medicines for rare diseases depending on the type of products will lead to faster generic/biosimilar competition. In turn, such a revision could also benefit the competitiveness of the EU industry in the global arena and attract investment for this innovation.

All options would introduce dedicated funding to support SME and academia, which will likely lead to more research in the realm of medicines for rare diseases and children.

Concerning **patients/health professionals,** it is expected that they will benefit from increased innovation and research especially in specific areas of unmet medical need**.**

Likely social impacts

All policy options are expected to have a positive impact on the quality of life of EU rare disease patients and children. The development of medicines for children and patients suffering from a rare disease will be boosted also in areas where treatments were not previously available. Moreover, all options aim to improve availability and accessibility to medicinal products for patients in the whole EU. Nevertheless, pricing and reimbursement will continue to remain of exclusive national competence and will therefore influence the actual availability and accessibility for patients.

All of the above would contribute to the improvement of the social inclusion of these patients (education, employment opportunities, etc.).

Likely environmental impacts

None of the policy options identified is expected to produce significant impacts, positive or negative, on the environment.

Likely impacts on fundamental rights

All policy options identified are expected to have a positive impact on the right of patients to have access to a high level of human health protection by making medicinal products available and more accessible in all Member States. Health disparities are expected to be reduced, as the aim is to offer the same quality of treatment to all EU patients, by making sure that children and patients affected by rare diseases are treated equally as any other patient.

Likely impacts on simplification and/or administrative burden

All policy options will include elements of simplification and reduction of administrative burden that is expected to benefit developers and patients. For example, they may bring about a more streamlined system identifying possible future medicinal products for rare diseases and a more flexible system to determine which clinical studies should be conducted in children. Moreover, all options would increase and simplify procedures and cooperation between the concerned Agency committees.

D. Evidence Base, Data collection and Better Regulation Instruments

Impact assessment

An impact assessment will be carried out to support the preparation of this initiative and to provide a robust evidence base for the contents of the legal proposal(s). The impact assessment is expected to run until Q1 2022.

The impact assessment will quantify, as far as possible, the costs and benefits of the changes described in the options presented above.

Evidence base and data collection

- A study will be commissioned to support the impact assessment process. It will be used to source additional evidence on the costs and benefits of the different policy options outlined. In particular, it will provide data on expected economic, social and administrative impacts.
- Data collected in the various studies and reports that have supported this evaluation (an 'orphan study, a 'paediatric study' and a study on the impact of the pharmaceutical incentives).

Consultation of citizens and stakeholders

Interested parties will be consulted through a mix of open and targeted consultations. Targeted stakeholders will cover the EMA, national competent authorities, pharmaceutical industry (including SMEs), civil society representatives (e.g. patients, public health organisations) and healthcare providers (e.g. professional associations).

A public consultation for citizens and all stakeholders will be launched during the first half of 2021 and will run for a period of 12 weeks. The questionnaire will be available in all 24 official EU languages and replies accepted in all these languages. The consultation will be accessible from the Commission's 'Have Your Say' portal.

A synopsis report on all consultation activities will be published on the consultation webpage together with the result of the assessment of impacts.

Will an Implementation plan be established?

No implementation plan is planned (the legislative instrument will keep the form of a Regulation and will therefore be directly applicable to/in Member States). Furthermore, the direct burden of implementation for Member States will be minimal, as most of the tasks will be conducted by the Agency and the Commission.