Feedback from the Netherlands and Belgium, participants in the Beneluxa initiative, on the Inception Impact Assessment of Revision of the EU regulations on medicines for children and rare diseases

6 January 2021

A. Joint statement from the Netherlands and Belgium

The Netherlands and Belgium welcome the opportunity to respond to the inception impact assessment from the European Commission regarding the EU regulations on medicines for children and rare diseases. We recognise that both EU regulations on medicines for children and rare diseases have been fruitful in the development of products addressing certain unmet needs, but in some aspects, the regulations have been inefficient (e.g. for certain diseases the regulations have not stimulated research and development) and could be improved. We fully support that the revision of both regulations must address the problems as set out in the inception impact assessment and stresses the need to:

- Focus more on development in areas of the greatest unmet medical needs for patients;
- Improving availability and accessibility in all EU Member States;
- Revise the regulations to make them "future-proof" for scientific and technological development;
- Take inefficient and burdensome procedures out of the legislations, as also identified in the recently published EU pharmaceutical strategy. However, this needs to be further developed.

We ask the Commission to perform the **impact assessment on each proposal separately and in combination**, so that the impact, specific characteristics, interferences and synergies compared to the current situation for each option are clear. The impact assessment should not only take into account the impact on innovation (i.e. research and development of medicinal products), but also the **impact on accessibility and affordability of medicinal products** and also on how market players will react.

To address **unmet medical needs**, the first step is to have a **clear and common understanding as well as an unambiguous definition with transparent criteria at the EU level** and to look closely at the **coherence** and **sequence of the actions in the pharmaceutical strategy** and in the orphan and paediatric regulations and incorporate this in the implementation plan of the pharmaceutical strategy.

Novel incentives must stimulate research and development of medicines for the greatest unmet medical needs, without a negative impact on accessibility and affordability.

We should carefully assess **the conditions for granting exemptions from the obligation to study all new medicines in children** in order **to avoid** that that the legislation will **limit innovation**.

Market exclusivity should be limited and variable; the company can apply for an extension and the maximum duration remains 10 years. If a company applies for extension of the period of market exclusivity, insufficient return on investment should become a standard criterion.

We support the proposal **to cumulate numbers of people** affected by all rare conditions targeted by the same orphan medicinal medicine and that it will **not be possible to obtain orphan designations for subsets of common diseases**.

The proposals to assess the **impact of changing the current threshold** of total number of cases at a specific time (prevalence), and also to **use a different criterion** to identify specific rare case (incidence) are welcomed.

Feedback from the Netherlands on the Inception Impact Assessment of Revision of the EU regulations on medicines for children and rare diseases

6 January 2021

A. General feedback

The Netherlands welcomes the opportunity to respond to the inception impact assessment from the European Commission regarding the EU regulations on medicines for children and rare diseases. We recognise that both EU regulations on medicines for children and rare diseases have been fruitful in the development of products addressing certain unmet needs, but in some aspects, the regulations have been inefficient (e.g. for certain diseases the regulations have not stimulated research and development) and could be improved. The Netherlands fully supports that the revision of both regulations must address the problems as set out in the inception impact assessment and stresses the need to:

- Focus more on development in areas of the greatest unmet medical needs for patients;
- Improving availability and accessibility in all EU Member States;
- Revise the regulations to make them "future-proof" for scientific and technological development;
- Take inefficient and burdensome procedures out of the legislations, as also identified in the recently published EU pharmaceutical strategy. However, this needs to be further developed.

B. Overall issues for pediatric and orphan medicines

1. Impact assessment

The Netherlands welcome the speed of the European Commission to start with an Impact Assessment in February/March 2021. A thorough impact assessment of all proposals is needed, which not only takes into account the impact on innovation (i.e. research and development of medicinal products), but also the impact on accessibility and affordability of medicinal products and on how market players will react. Therefore, we ask the Commission **to perform the impact assessment on each proposal separately and in comparison with each other**, so that the impact compared to the baseline situation for each option is clear. There is a risk that **coherence** is lost if there a too many simultaneous changes in the regulation.

2. Unmet medical needs

In the process leading to the EU pharmaceutical strategy, in the Dutch responses to the public consultation of the roadmap and pharmaceutical strategy itself and more recently in the joint declaration of 17 countries (attached)[1] to provide the European Commission with input, the Netherlands has stressed the need to discuss the term **unmet medical needs**. In the specific context of the evaluation of the paediatric and orphan regulation, the Netherlands repeats the need for **a clear definition and common criteria** at the EU level for defining **unmet medical needs** which will be the basis for further refinement for e.g. medicines for children and rare diseases, but also for antibiotics and other disease areas. In this discussion, the question whether off-label use of medicines does or does not address the unmet medical need, should also be included.
In addition, it is important to identify the **root causes** of unmet medical needs and determine whether for example the scientific knowledge of the disease is lacking, or that the market is unattractive. **Different root causes will need different solutions**. The European Commission does not propose a clear definition or common criteria for unmet medical need in the inception impact assessment. This is necessary though for the follow up of the process of the revision of both regulations and the implementation of the pharmaceutical strategy. Furthermore, the inception impact assessment and the implementation of the pharmaceutical strategy intersect, so it is therefore crucial to look closely **at the coherence and sequence** of the actions in the

[1] **#Prescription4EU – Five remedies for a Pharmaceutical Strategy for Europe catering for national health systems and patients' needs** *by Austria, Belgium, Croatia, Estonia, Finland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Portugal, Romania, Slovenia, Sweden and the Netherlands.*

pharmaceutical strategy and in the orphan and paediatric regulations. This needs to be incorporated in the implementation plan of the pharmaceutical strategy.

3. Novel incentives

Novel incentives are proposed in the inception impact assessment, however no clear examples or indication of potential incentives are described. Still, the Netherlands is interested in exploring potential novel incentives. In that context, novel incentives should be tailored to address the root causes of unmet medical needs. For example is scientific knowledge of the disease lacking, or is the market unattractive and if so, why? After defining the novel incentives, each of its impacts must be assessed adequately in order to avoid any undesirable negative implications on accessibility and affordability of medicines. It is therefore of utmost importance that novel incentives do stimulate research and development of medicines for **the greatest unmet medical needs, without a negative impact on accessibility and affordability**. This seems more difficult for the proposed transferable vouchers, because of its complexity.

4. Generic and biosimilar competition

The inception impact assessment focuses on improving availability, accessibility and affordability by fostering earlier **generic and biosimilar competition** for both paediatric and orphan medicines. We do welcome this, since generic and biosimilar competition is important for the sustainability of the health budget. However, the question is whether the markets of some paediatric and orphan medicines are not too small, which makes them unattractive for a second player. The Netherlands therefore requests to take this into account in the impact assessment, and include other options to stimulate competition in these specific markets.

5. Common elements

We welcome the **common elements of all policy options** that are presented for both regulations, such as 1) **the focus on unmet medical need,** 2) **enhanced regulatory support,** 3) **better catering for scientific and technological developments** and 4) **the exploration of improved rules for linking rewards with the obligation to launch on most/all Member States' markets**. At the same time, we also acknowledge that the impact of specifically the latter element should be carefully studied to avoid negative implications. The Netherlands would therefore be interested in having a discussion on how to achieve market introduction in most/all EU Member States in a minimal burdensome way for companies and reimbursement authorities.

C. More specific feedback

1. Paediatric regulation

The submission of a Paediatric Investigation Plan (PIP) is obligatory for all medicinal products, however at the same time not all medicinal products qualify for a Supplementary Protection Certificate (SPC), because it contains a known active substance, or still have a SPC at the time of the paediatric application. **The incentive of a paediatric SPC extension is thus linked to an obligatory action, without the possibility of all medicinal products benefitting from it**. An incentive should stimulate research and development in a certain area and the current paediatric SPC extension has been useful in stimulating research and development with existing medicines in children to catch up the backlog. But now that the backlog for existing products is eliminated, and the submission of a PIP for a new application is an obligation, the **current paediatric SPC extension is no longer considered a true incentive that stimulates research and development**. The impact of scrapping the current paediatric SPC extension as main reward for the completion of the obligatory PIP without additional conditions such as linkage to placing on the market in most/all Member States or limitation to medicines addressing unmet needs for children should be assessed, in line with the 1st, 2nd and 4th option. The impact assessment should also closely look at the number of medicines not qualifying for a SPC and therefore not benefitting from this incentive, even if the product is placed on the market in most/all Member States or if the product addresses unmet needs for children. The impact assessment should also take into account the number of paediatric patients actually treated with the product.

The Netherlands believes that we **should carefully assess the conditions for granting exemptions from the obligation to study all new medicines in children in order to avoid that the legislation will limit innovation**. The purpose of limiting the exemption is to ensure that products that could be beneficial for children due to their mechanism of action will be investigated in another indication as aimed for in the adult population. However, this could lead to undesirable implications such as forcing a company to study a medicine in a completely different indication as originally aimed for (possibly an indication for which the company has no or only limited expertise), which could restrain a company from submitting an application.

In line with the proposal for the orphan regulation to vary the duration of market exclusivity depending on the type of application (which relates to the research and development activities), the Netherlands is of the opinion that this should also be the case for the paediatric incentives. For example if a **medicinal product is already used off-label in children**, and this is described in peer reviewed literature or in treatment guidelines, **the product should not be able to qualify for the full period of extra protection** after approval for a paediatric indication.

2. Orphan regulation

The Netherlands has longer been of the view that **variable durations of market exclusivity under conditions** could apply. We are therefore interested in the proposal that in principle market exclusivity will be limited to for example 5 years after which the company can apply for an extension under certain conditions. The length of market exclusivity for repurposed orphan medicinal products (i.e. a known active substance already used off label for an orphan indication that obtains a marketing authorisation) should be shorter than for innovative products, as in general R&D activities were limited.
If a company applies for **extension of the period of market exclusivity,** insufficient return on investment should be considered as a standard criterion for extension of this period of market exclusivity, where the burden of proof should be on the company-side and full transparency is required. It must be ensured that procedures will be efficient, not burdensome and will actually benefit innovation and competitiveness. For this option, we should agree beforehand what data needs to be submitted, and how these will be assessed.

The Netherlands also supports the proposal to **cumulate numbers of people** affected by all rare conditions targeted by the same orphan medicinal medicine and that it will not be possible to obtain orphan designations for **subsets of common diseases**.

We welcome the proposal to assess the impact of changing the current **threshold** of total number of cases at a specific time, and the proposal to use a **different criterion to identify specific rare cases**, for example on the basis of incidence instead of prevalence for granting an orphan designation. However it must be clear which medicines will no longer meet the new criteria, and what the consequences will be on the development of these products. The impact of the proposal **to change the threshold combined with novel incentives**, seems to be difficult to assess and should therefore get specific attention in the impact assessment.

The impact of a **temporal validity of an orphan designation** should be carefully assessed. If the company gives a good justification why a designation is not followed by the development of a medicinal product, the designation should remain valid. The information of the reasons behind the delays or lack of the development of a medicinal product could be of great value. A system to keep track of this information could be used to identify the causes for unmet medical needs and correctly stimulate further research & development. For example if several companies have an orphan designation for a certain condition, and the reason for delay lies in the fact that scientific knowledge is lacking, then ways to stimulate research & development in that condition is needed.

The Netherlands is of the opinion that first **clarity** is required on the **criteria for unmet medical need** and on the **novel incentives** before a preference for an option can be given.

Conclusion

The Netherlands agrees that there is room for improving the paediatric and orphan regulations on the identified problems proposed by the Commission in the inception impact assessment. We support that the Commission is taking concrete and **fast steps forward** to revise both regulations on aspects the Netherlands has addressed in the past. At the same time, we also urge the Commission to be mindful on the **right sequence and coherence** in the study of the impact assessment, without making redundant delay. The most urgent matters are therefore in our view (1) the discussion of **unmet medical need broader than the orphan and pediatric products** and **simultaneously** with the discussion in context of the **pharmaceutical strategy** and (2) identifying the **root causes** of unmet medical need to tailor the **right novel incentives**.

#Prescription4EU – Five remedies for a Pharmaceutical Strategy for Europe catering for national health systems and patients' needs

** Austria, Belgium, Croatia, Estonia, Finland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Portugal, Romania, Slovenia, Sweden and the Netherlands have identified the following common priorities and next steps, which need to be further discussed at the European level in the context of the strategy implementation and the long term partnership[1] between the European Commission and the Member States [2].*

1. To **tackle Shortages** collectively and **build a European response**.

Points to be discussed as soon as possible are:

- Encourage more solidarity and cooperation by agreeing to common principles towards building sustainable stocks at different levels of the supply chain. Consider strategic reserves at EU level for medicines for human use and medical devices, foreseeing mechanisms for access and equitable distribution.
- Coordinate measures at national and European level to: (1) generate best practices in monitoring and data management as well as in stakeholder interaction and communication, and (2) improve early notification of supply disruptions and investigating their root causes. This includes evaluating the effectiveness of joint EU public procurement and its potential use for better distribution of medicines.
- Emphasize obligations of marketing authorisation holders and wholesalers to ensure the security of supply and explore tools available to uphold such obligations, for example discussing mandatory risk mitigation measures.

2. To **define** clear criteria for '**Unmet Medical Needs'**, appropriately **stimulating and rewarding innovation** while securing a healthy pharmaceutical market and the sustainability of healthcare systems.

Points to be discussed as soon as possible are:

- Identify the target conditions, technologies or patient groups that new therapies are to focus on over a given timeline.
- Evaluate ongoing private and public innovation incentives and funding to drive future clinical R&D to meet patients' needs.
- Tackle the global health threat of antimicrobial resistance (AMR), by stimulating prudent use, strengthening incentives for R&D of new antimicrobials, their alternatives and diagnostics; using the potential of EU instruments, structures and policies to explore new models for research, development, production and purchasing, to stimulate the availability of (new) antimicrobials.
- Stimulate pharmaceutical companies to maintain older medicinal products on the market by creating better incentives for medicines' repurposing, reducing the regulatory burden and stimulating the introduction of electronic product information and multi-language packaging.

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[1] See joint Non-paper by Austria, Belgium, Croatia, Cyprus, Estonia, Finland, Ireland, Italy, Lithuania, Luxemburg, Malta, Norway, Portugal, Romania, Slovenia, Spain, Sweden and the Netherlands on a joint vision for a Pharmaceutical Strategy for Europe.

[2] The content of this declaration is without prejudice to national positions. The above-mentioned points are to be discussed in greater detail and therefore Member States reserve the right to submit additional and/or other viewpoints, subject to the actual content of the pharmaceutical strategy for Europe to be published on 24 November 2020.

3. To **redesign** the **framework** for **Advanced Therapy Medicinal Products (ATMPs) and create a system equipped** to **respond to** scientific and technological **developments**.

Points to be discussed as soon as possible are:

- Review and update the regulatory framework for ATMPs. The two available routes - central registration and hospital exemption – play an important role with certain ATMPs, but respond inadequately to all scientific and technological developments.
- Discuss thoroughly whether current marketing authorisation procedures are fit for personalized medicines.
- Share best practices in hospital exemption procedures; discuss whether the hospital exemptions would benefit from review and harmonization across the EU, also in regards to pharmacovigilance.

4. **To create a Pharmaceutical Hub in Europe** to **reinforce** the region's **capacity.**

Points to be discussed as soon as possible are:

- Emphasise EU's role in the global pharmaceutical production and supply chain, considering how to stimulate R&D, optimise the supply chains, diversify sourcing and suppliers, tackle environmental and waste water aspects, and stimulate innovative, cleaner and sustainable local pharmaceutical production.

5. To **foster International Cooperation -** while bearing in mind national competences - to **achieve** equally **accessible, affordable medicines.**

Points to be discussed as soon as possible are:

- Encourage information exchange throughout the product's lifecycle between regional collaborations and individual Member States, paving the way to coordination and collaboration in the field of HTA and pricing and reimbursement, thereby promoting better alignment in the measurement and analysis of health outcomes of interest and achieving a more balanced pharmaceutical market.
- Look into legislative and non-legislative actions at EU level aiming to reduce asymmetries in access across the single market and encourage healthy competition.