

Annex to 1098252/161409/GMT (April 3<sup>rd</sup>, 2017)

Ref. PCPM/16 — Paediatric Report

Public consultation on the Paediatric Regulation.

Dutch government response to the Public Consultation on the Commissions report on the Paediatric Regulation

## Introduction

This document contains the response of Dutch Government to the Commission's report on the Paediatric Regulation.

The Paediatric Regulation<sup>1</sup> was adopted in 2007 to address a serious gap in knowledge on how medicine should best be used by children.

Many products administered to children were prescribed and administered based on experience (off-label) rather than on the results of clinical research. The Paediatric Regulation therefore aims to reduce the level of off-label use and increase the number of medicines specifically developed and tested for children. To do this, it sets up a system of obligations, rewards and incentives, and puts in place measures to ensure that medicines are regularly researched, developed and authorised to meet children's therapeutic needs. The Regulation obliges companies to agree a paediatric research and development programme ('paediatric investigation plan') with the European Medicines Agency (EMA) for every new product they develop. One of the Regulation's undisputed achievements is bringing more attention to paediatric development. Companies now consider it an integral part of overall product development.

The Ministry of Health and the Medicines Evaluation Board (MEB) of the Netherlands welcome the consultation on the Paediatric Regulation of the European Commission. In general the Paediatric Regulation supports the development of medicines for children and pin points the long-standing problem on paediatric research needed for marketing authorisation. The Dutch government would like to underline some key concerns notwithstanding the expertise and work done by the Paediatric Comite (PDCO) and within the Member States, in the hope that future amendments of the Regulation or additional incentives can give a rise to the availability of paediatric medicines.

### 1. More medicines for children.

Consultation item No 1: Do you agree that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines?

#### Response

The Netherlands does agree specific legislation is needed, but current legislation does need to be evaluated.

The goal of the Paediatric Regulation is better medicines for children, by ensuring high-quality research, reducing off label use and increasing the availability of age appropriate formulations and

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<sup>1</sup> Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (PbEU L 378)

finally to share knowledge about medicines used by children. And in case off label use is a last resort then only with data based on clinical trials or well established use.

One point of interest of the Paediatric Regulation is that the paediatric development is always linked to the adult development. A MAH is obligated to submit a PIP for indications related to the adult development of the product. For example in case the biological indications in children differ from the adult indications. Another example is oncolytics for all indications in the different tumours. In those cases, the MAH needs to submit a waiver for each type of tumour whereas there is no incentive to develop a paediatric indication. That is because basket trials for all related indications are not possible yet. In this respect there is a legal obligation to submit a PIP or waiver request, however there is no legal obligation to submit a paediatric only indication, even when there is a medical need.

To illustrate, clinicians and pharmacies let us know that there is (still) a lack of adequate paediatric formulation. This was also high lighted and addressed by guest speakers at the informal Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh) during the Dutch EU presidency in 2016. It was discussed that if a product is already registered and marketed for adults, there is no incentive to apply for a specific paediatric indication. Even if the adult indication is similar to the paediatric indication and use of the medicine in children is considered rational, there is still a need for age appropriate formulations. For instance a liquid formulation or smaller tablets might be needed before the medicine can be administered to a child. There is a special demand for liquids of antiepileptic medicine ( phenobarbital, phenytoin, lamotrigine);

There is no legal pressure to develop medicines for paediatric only indications. Therefore, the Regulation stimulates mainly the development of medicine in children for therapeutic areas where there is in first instance a need in the adult population even though there is a high unmet medical need for children. This leads to a delay in the development of new medicines for paediatric oncology. Many tumour types (indications) only occur in adults, therefore the need for a PIP might be waived. Also the MAH is not obligated to examine the use of the product in tumour only occurring in children, whereas activity in paediatric oncology might be anticipated due to the mode of action.

## 2.Mirroring paediatric needs

Consultation item No 2: Do you have any comments on the above? To what extent and in which therapeutic areas has the Regulation contributed to the availability of important new treatment options?

### Response

The Regulation has put the treatment of children and the importance of paediatric medicines on the agenda of Europe. However due to the fact that there is no legal incentive to develop medicines for paediatric only indications, there is a trend that new paediatric treatments are developed mainly in areas where there is a need in the adult population.

## 3.Availability of paediatric medicines in the EU

Consultation item No 3: In your experience, has the number of new paediatric medicines available in Member States substantially increased? Have existing treatments been replaced by new licensed treatments?

### Response

Although the real number of available paediatric medicines is not known, it seems the number did not substantial rise.

The exact number of paediatric medicine that are available is not known to the Dutch authorities, nor to what extent the availability has changed after the Regulation entered into force. Although the Paediatric Regulation does exist 10 years, a minority of the PIPs that are approved has been completed, because of the long duration of clinical (paediatric) studies and the high amount of approved deferrals for PIPs. Therefore the full impact of the Paediatric Regulation on the availability of paediatric medicines and the off/on label use of medicines by children, is not clear.

With the development of an age appropriate formulation: age range among children, dosage, accuracy, volume and excipients, should be considered. From the discussion at the CMDh in Utrecht currently several action points were formulated. The Netherlands will be engaged to investigate ways/procedures to get a marketing authorisation in the Member States where the product is needed and not authorised yet in a more efficient way than usual repeat use procedures.

#### 4. Reasonable costs

Consultation item No 4: Do you have any comments on the costs for pharmaceutical companies to comply with an agreed paediatric investigation plan?

#### Response

The Dutch pharmaceutical authorities share the view that incentives for the MAH could help to stimulate the development of medicines for children to compile a PIP, develop an age appropriate formulation and conduct the non clinical and clinical studies to comply with the PIP.

In addition it seems deceptive to extrapolate the average amount per agreed PIP (€ 20 million) while this means it includes the costs for not completed PIPs. To comment though on the reasonability of this figure you need to compare it to the costs for other medicines similar to the paediatric product, and to the benefits for both. Benefits do depend on several wide ranging aspects, which makes this discussion about the reasonability of the costs highly conceptual.

#### 5. Functioning reward system

Consultation item No 5: Do you agree that the reward system generally functions well and that early, strategic planning will usually ensure that a company receives a reward?

#### Response

It seems difficult to answer these questions. Whether the reward system is functioning depends on several aspects: did the company recuperate the costs?, did the company recuperate the costs even significantly? did the rewards lead to a rise in available paediatrics?

In addition the Dutch Authority for Consumers and Markets<sup>2</sup> conclude that pharmaceutical companies in some cases use the reward system to prevent generic medicines to enter the market. This is regarded highly unwanted. Therefore, the Dutch departments for Health, Welfare and Sport and for Economic Affairs plan to commission a study into the effects of supplementary protection certificates, SPCs. This study will specifically focus on medicinal products and investment aspects. Moreover it will focus on the interaction between legislation and the way the pharmaceutical market is organized, where this interaction could lead to unwanted effects. The results will probably be available in Q2 of 2017. We will inform the Commission in due time.

In the system of the paediatric legislation the reward is provided after the PIP is completed. Even when the outcome of the study is not positive the reward will be granted (as these data are still relevant). With regard to the SPC, the benefit for the MAH is the greatest when the sales figures are highest, mostly due to use in adults. Therefore, MAH developing blockbusters for adults are most stimulated to complete a PIP on time. MAH who develop products in areas with high

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<sup>2</sup> Autoriteit Consument en Markt, 2015. Farmacie onder de loep, 25 p.; [www.acm.nl](http://www.acm.nl)

paediatric unmet medical need and relatively low sale in the adult population obtain less benefit by the reward system. This phenomena shows that the reward system is not driven by unmet medical needs in children.

A medicinal product with orphan designation having received a positive opinion of the CHMP (for marketing authorization) and a positive opinion of the COMP (for maintaining the orphan status) will be rewarded 2 years extra market exclusivity in the EU when the PIP is completed. In most cases however the PIP is not yet completed at the time of MAA, either because of a deferral or due to the need for additional safety data. This means the MAH is not rewarded.

This all means that MAHs are most probably not highly motivated to start a paediatric study for products that might fulfill an unmet medical need in children but that are not often used in adults. In that case the final paediatric indication will most probably not be a blockbuster. In addition conducting such a study is not easy due to for instance ethical reasons and low number of patients.

#### 6.The orphan reward

Consultation item No 6: How do you judge the importance of the orphan reward compared to the SPC reward?
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##### Response

The relation between orphan and SPC reward is complicated. The choice of the MAH for either reward depends on many factors and at the end will influence the availability of paediatric medicines. When the disease occurs predominantly in the paediatric population, the PIP may have been completed at the time of MAA. A 12 years (10 + 2) market exclusivity may then become attractive for the MAH. So far only a few orphan medicinal products have received this reward, indicating that it may be either not so realistic to achieve or not that important for the MAH.

In other cases there are examples of products (Glivec) for which the orphan designation was withdrawn to be able to submit for the SPC reward. Apparently this was more attractive because the global marketing authorization could then include more indications than the rare disease indication only.

#### 7.Improved implementation

Consultation item No 7: Do you agree that the Regulation's implementation has improved over time and that some early problems have been solved?
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The Netherlands agrees that several measures implemented after publication of the Regulation have led to an improved performance. We would welcome the proposed simplification in PIP formulated by the EMA – indeed key binding elements are decreased.

In brief, the obligation for the submission of a PIP is not an efficient system. In the end MAH will have to submit a PIP in a very early phase to ensure that with a stepwise approach adjustments can be made and relevant data for a possible paediatric indication can be collect (when the efficacy and/or effectiveness for the specific indication is known). At this early phase the product's exact mode of action and potential use is not always clear. Therefore most PIPs are modified a number of times after the first PIP opinion. This is especially the case when a PIP includes many details. Whereas if the MAH submits the PIP in a rather late phase several modification and deferrals should be submitted.

It has been suggested to change the system. For instance at first agreeing on basic principles instead of the complete PIP at the moment of early submission. After agreed milestones of the product development are reached the MAH is able to submit modification/refinements of the PIP.

It should be noted there is not always an incentive for the MAH/applicant as there is no legal obligation for the applicant to revise the PIP. This happens in case of a safety issue or only 1 subpopulation in adults during the development. The PDCO can request for an update in the PIP; however there is no legal obligation for the MAH to act upon this request.

#### 8. Waivers and the 'mechanism of action' principle

Consultation item No 8: Do you have any comments on the above? Can you quantify and qualify missed opportunities in specific therapeutic areas in the last ten years?
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##### Response

Any measure to avoid unnecessary research with patients or volunteers is regarded of undisputable importance. However, it is unacceptable that applying waivers leads to persistence of unmet medical needs in children, like in paediatric oncology. Whether there are other medical areas where this happens needs further investigation.

#### 9. Deferrals

Consultation item No 9: Do you agree with the above assessment of deferrals?
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##### Response

The Netherlands accepts that in some instances it could be useful to delay the initiation of a trial with children until more data is gathered in adults trials. The Paediatric Regulation includes provisions to request for such a deferral of data/studies in a PIP, which request the PDCO always can reject.

However, such a delay could also have negative effects on the availability of medicines for children. For instance, if the start of a paediatric study is deferred till after approval of a marketing authorisation, initiation is often complicated because physician, parents and patients might be inclined to use the product off label instead of participating to a clinical study. Furthermore, there are no legal obligation to start a paediatric study when the submission of the MA has already taken place. From that moment on there is no other way to enforce the MAH to complete the PIP.

#### 10. Voluntary paediatric investigation plans

Consultation item No 10: Do you have any comments on the above?
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##### Response

The Netherlands has no specific comments on this item.

#### 11. Biosimilars

Consultation item No 11: Do you have any comments on the above?
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##### Response

The Netherlands has no specific comments on this item. The number of submitted PIPs for generic medicinal products is rather low. Within the framework of paediatric medicinal products the Netherlands does not have any concerns about biosimilars.

#### 12. PUMA – Paediatric-use marketing authorisation

Consultation item No 12: Do you share the view that the PUMA concept is a disappointment? What is the advantage of maintaining it? Could the development of off-patent medicines for paediatric use be further stimulated?

Response

The Netherlands agrees that the effect of the PUMA-concept is rather falling short.

The Netherlands is in favour of the stimulation of the development of off-patent medicines for paediatric use, however there is not much incentive for Marketing Authorisation Holders to submit data of an off patent drug for *exclusive* use in the paediatric population. As the product authorised under PUMA will be *exclusively* used in the paediatric population, the price of the product will become relatively high compared to the already registered product for adults. Health care professional rather will prescribe the latter to children, however off label (the MA for adults). Therefore PUMA will not become economically beneficial because off label use is allowed without any clinical studies.

13. Scientifically valid and ethically sound – Clinical trials with children.

Consultation item No 13: Do you have any comments on developments in clinical trials with children following the adoption of the Regulation and in view of the above discussion?

Response

The clinical trial EU-legislation is in place to ensure protection of vulnerable (patient) groups, like children. Ethical committees should be aware of their key role in this protection framework. In addition registration and inspection authorities should be focused equally on scientific and ethical aspects of clinical trials that are used for marketing authorization application. This focus should not be limited to clinical trials that are performed in EU member states, but should treat trials in third countries equally if they are part of the MAA dossier.

The Netherlands is of opinion that there are certain other aspects of research with vulnerable populations that could enhance the use of available research data, for instance; interlinked health care databases, shared methodologies to retrieve paediatric information, and standardised methods and study designs. In addition, the focus should be much more towards new approaches into the development of standardised methodologies instead of voluntary PIPs.

14. The question of financial sustainability

Consultation item No 14: Do you have any views on the above and the fact that the paediatric investigation plan process is currently exempt from the fee system?

Response

The Netherlands is of the opinion that the assessment and adjustments of the PIP requires a substantial amount of time and expertise from the members of the PDCO and therefore also from the staff of the NCAs that supports them. Besides the work within the PDCO there is close cooperation with the COMP, CHMP, CMDh and PRAC. Currently there is no reimbursement for the members of the PDCO (except for the chair and co-chair) nor for the working hours put in by the staff of the NCAs. To facilitate and ensure that the burden of assessments and adjustments of PIPs and waivers is rewarded, the members of the PDCO and therefore also staff of the NCAs should be reimbursed. In practice it would mean that for NCAs it would be possible to send an alternate to the PDCO and that there is more time to bundle the expertise with a focus on paediatric developments.

The evaluation of the Fee Regulation should then involve these discussions about the reimbursement of the costs for the deployment of PDCO delegates and the NCA staff within the framework of the Paediatrics Regulation.

#### 15. Positive impact on paediatric research in Europe

Consultation item No 15: How do you judge the effects of the Paediatric Regulation on paediatric research?

#### Response

The Netherlands has no specific comments on this item.

#### 16. Mirror, mirror on the wall – Emerging trends and the future of paediatric medicines

Consultation item No 16: Are there any emerging trends that may have an impact on the development of paediatric medicines and the relevance of the Paediatric Regulation?

In the view of the Netherlands there are no other trends than already mentioned in the paper, including the “mechanism-of-action principle (see item 8).

#### 17. Other issues to be considered

In our view the Regulation and its performance still needs improvement as long as there are still unmet medical needs for children and needless medicines for children at the same time. Also the effect of the rewards on the availability of paediatric medicines could be more substantiated.

With regard to the cost of the Paediatric Regulation not only the cost for the MAH but also the cost and capacity for the NCAs should be considered. For a thorough assessment and discussion of the PIP and the study results received at completion of the studies included in the PIP's, also investments of NCAs are requested. Special attention should be given to the cost of the many modifications of a PIP that might be needed to adjust a PIP that is agreed at the moment that fundamental knowledge of the product and the potential indications is not yet available.

Finally, filling up the knowledge gap on efficacy in children and on cost/benefit ratio we think is also a point of concern. In this context we observe that the PDCO has mainly been focused on PIPs applications and scientific advices due to the legal obligations and incentives in the Regulation. It is regarded by the Dutch authorities of great importance to mobilize all the knowledge, skills and experience acquired by the PDCO and her members in order to ensure that new medicines are available for children in a timely manner.