Consultation in relation to the Paediatric Report

Ref. PCPM/16 – Paediatric Report

1. PART I - GENERAL INFORMATION ABOUT RESPONDENTS

Your name or name of the organisation/company: Health Products Regulatory Authority (HPAR)

Transparency Register ID number (for organisations): _____

Country: Irish_____

E-mail address:
PQsandBriefings@HPRA.ie_____

Received contributions may be published on the Commission's website, with the identity of the contributor. Please state your preference:

- **My contribution may be published under the name indicated; I declare that none of it is subject to copyright restrictions that prevent publication**
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Please indicate whether you are replying as:

- A citizen
- A business
- A non-governmental organisation (NGO)
- An industry association
- A patient group
- A healthcare professional organisation
- Academia or a research or educational institute
- **A public authority**
- Other (please specify)

If you are a business, please indicate the size of your business

- Self-employed
- Micro-enterprise (under 10 employees)
- Small enterprise (under 50 employees)
- Medium-sized enterprise (under 250 employees)
- Large company (250 employees or more)

Please indicate the level at which your organisation is active:

- Local
- National

- Across several countries
- **EU**
- Global

2. PART II – CONSULTATION ITEMS

(You may choose not to reply to every consultation items)

2.1. 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?

It is evident that the paediatric regulation has promoted the development of paediatric medicines in a way which heretofore had not occurred. There is no evidence that such developments would continue should the regulation be revoked. The nature of both the paediatric population and the relative rarity of diseases in that population are such as to limit the financial rewards accruing from developing paediatric medicines.

This is also relevant to the development of age-appropriate paediatric formulations, such as liquids or smaller sized tablets, as the children most likely to benefit from the availability of such formulations often represent the smallest cohort of those affected by the particular disease or condition. As such, the return on investment for that particular formulation is often less than might be expected for other formulations more suited to older children or adults.

As such, it seems appropriate that specific legislation supporting the development of paediatric medicines is necessary to ensure the continuation of the development of safe, effective and age appropriate medicines for children.

2.2. 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?

The paediatric regulation stipulates that the adult condition is the starting point for the paediatric development. This can have the perverse outcome of artificially limiting the paediatric development. If the adult condition is one which does not occur in children, then no development is required, even if the mechanism of action of the product is such that different but related conditions in children would be amenable to treatment.

Many examples of this can be found and the situation in paediatric oncology, for example, has been well described by the various professional representative bodies in the field (SIOPE submission to the European Parliament). Another example is that of age-related macular degeneration (AMD), a condition associated with advancing age. The pathophysiology of AMD is very similar to a rare paediatric disease, Stargardt's disease, but developers of medicines for AMD are not obliged to investigate the utility of their products in this condition. This can lead to the medicines being used in an off-label manner without the presence of data to confirm the efficacy or safety of the medicine in that condition.

The paediatric regulation also stipulates that the adult marketing authorisation should not be delayed by the paediatric development. This can have the effect of the paediatric development being hindered by the

availability of the medicine (albeit unlicensed in children). This can then make recruitment to paediatric clinical trials less feasible, as parents become reluctant to enter their children into trials where they fear they might be allocated away from the medicine.

2.3. 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?

Information on the number of new medicines authorised in the member states is contained within the 10 year report on the functioning of the Paediatric Regulation (here). Overall, this Regulation has been successful in increasing both the number of new medicinal products for children and in increasing the number of age-appropriate formulations for use in the various paediatric populations.

It is unclear how well these medicines have been taken up by healthcare providers, as this information is often unavailable to authorising authorities but instead rests with prescribers and reimbursement bodies. It is certainly hoped that patients can benefit from the increased availability of properly tested and formulated paediatric medicines.

2.4. 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?

This is not within the remit of HPRA, however there are financial incentives offered to companies for scientific advice and paediatric development (see additional responses below).

2.5. 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?

Early engagement with the regulation and a paediatric development plan is essential in ensuring that procedures and processes can be agreed and completed within the timeframe of the existing patent protection period. Occasionally, applicants leave the consideration of a paediatric development to late in their overall development. As such, they are then under pressure either to complete their plans or to secure a deferral of the completion of the paediatric development from the Paediatric Committee (PDCO) at the European Medicines Agency. Granting of such deferrals can have the effect of subsequently interfering with the paediatric development, as described previously.

The various competent authorities have put in place mechanisms to help developers engage at an early stage and developers are encouraged to use all these mechanisms. Many of these are free of financial cost to developers, which is an added incentive to them to use these processes. Such early engagement can help

reduce the risk of inappropriate developments taking place, which would have the possible effect of wasting both time and other resources on the part of the developer, as well as risking the rejection of the data produced from such developments at the marketing authorisation application (MAA) stage.

The European Commission is currently performing an economic analysis of the regulation, and the results of this analysis are expected soon. A similar analysis was performed following the introduction of paediatric legislation in the US, and the results of this seemed to show that applicants could expect a financial reward from the appropriate development of a paediatric medicine.

2.6. The orphan reward

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

In terms of the SPC reward, a six-month additional extension is available in accordance with Regulation (EC) No 1901/2006 if the SPC relates to a medicinal product for children for which data has been submitted according to a paediatric investigation plan.

The 10 year period of market protection is extended by 2 years for orphan medicines that have also complied with an agreed paediatric investigation plan granted at the time of review of the orphan medicine designation. This therefore is considered to be of high importance.

2.7. 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?

From a regulatory perspective considerable efforts have been made to facilitate companies' entry into and use of the system. In addition to this, efforts have been made to try to reduce the regulatory inconstancies which can occur between different procedures over time, and to reduce the differences between the regulatory requirements of different Competent Authorities in the different global regions.

Closer collaboration between the various major global regulatory authorities has helped applicants conduct multinational developments, which can be essential when it comes to recruitment of patients, particularly in rare diseases. This also has the effect of streamlining applicants' potential authorisation procedures, as the authorisation requirements become more closely aligned.

Closer internal collaboration and engagement has led to better communication between the various committees and working parties of the various regulatory authorities, which in turn has led to better consistency in the opinions taken by those agencies

The setting up of the pan-European paediatric research network, ENPR-EMA hopefully has led to better collaboration and resource utilisation between paediatric networks.

2.8. 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?

Clearly some medical conditions do not occur in children and therefore waivers are accepted, for example, for the development of medicinal products used in dementia. Similarly some products have a demonstrable safety concern in all or part of the paediatric population or would not provide significant therapeutic benefit over existing treatments. At the time the paediatric regulation was being drafted, it was considered inappropriate to require developers to investigate the use of such products in the paediatric population, as that population would not derive any benefit from such development.

The problems surrounding the regulation's insistence that the adult condition be the basis for the paediatric development are well described and have been referred to in previous answers above. Part of the problem may lie in the way diseases are classified, as this has a direct impact on how the condition itself is defined. A particular example is oncology, where diseases have traditionally been classified according to their anatomical distribution or histological characteristics. As certain cancer types only occur in adults, paediatric development is not mandatory according to the regulation, regardless of whether there are any similarities between the pathophysiology of the various conditions.

While the European Court of Justice (ECJ) ruling in the case of Nycomed vs EMA (Case T-52/09, December 2011) expanded the scope for the classification of diagnostic products, it is not clear whether such an interpretation could be applied to therapeutic medicinal products. Indeed, the ECJ specifically stated that therapeutic and diagnostic products differ in their nature, and therefore suggested that they should be treated differently under the regulation.

2.9. Deferrals

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

Yes. The concept of deferrals was intended to both protect the paediatric population and prevent unnecessary delays to the authorisation of adult medicines. Any requests for a deferral must be justified on scientific and technical grounds or on grounds related to public health. Unfortunately, as some applicants have presented very late with their development plans, the argument to defer the completion of the paediatric development has been frequently used to prevent unnecessary delays. Unfortunately this has led to difficulties in the conduct of paediatric clinical trials, as described.

The concept of unmet medical need has been postulated as a way of getting around this problem. While it is not ideal to delay the authorisation of adult-directed medicines, the greater unmet medical need in children can be an argument to decline the request for a deferral, thus requiring applicants to complete the paediatric development prior to their adult application.

This problem will hopefully be improved as applicants consider paediatric development earlier in their overall product development strategy, thus allowing themselves enough time to complete an appropriate development in all appropriate populations.

2.10. Voluntary paediatric investigation plans

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

It is understood by the HPRA that there have been very few voluntary paediatric investigation plans. It is common, when applicants come for a confirmation of a class waiver for their product, that alternative conditions for which the product might also be useful are highlighted to the applicant, with an invitation to submit a PIP for consideration. To my knowledge, no such invitations have been acted upon. This supports the opinion, stated in the answer to Question 1, that without the obligation to conduct paediatric development, market forces will remain insufficient to drive suitable development in this population.

2.11. Biosimilars

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

Biosimilar medicines are being developed as the innovator products are now coming off patent.
Regulatory authorities apply stringent criteria in their evaluation of the studies comparing the quality, safety and effectiveness of the two medicines. The studies on quality include comprehensive comparisons of the structure and biological activity of their active substances, while the studies on safety and effectiveness should show that there are no significant differences in their benefits and risks, including the risk of immune reactions in a sensitive population. Extrapolation of indications is allowed for however additional data are required in certain situations, such as:

1. The active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indications

2. The active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications

3. The studied therapeutic indication is not relevant for the others in terms of efficacy or safety, i.e. is not sensitive for differences in all relevant aspects of efficacy and safety.

Extrapolation of immunogenicity from the studied indication/route of administration to other uses of the reference product should be justified.

2.12. 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?

The PUMA concept has been a disappointment. There appears to be an understanding that PUMA applicants have difficulty in protecting the data exclusivity, such that investment in the concept is unprofitable. Even if a paediatric-specific formulation can be authorised and marketed, there is no guarantee that end users will use

this formulation over cheaper, unlicensed versions. This is a situation which has been replicated with other regulations, such as the Orphan medicines regulation.

There has been some progress in helping potential PUMA applicants navigate the regulatory process. The adoption of targeted waivers has helped applicants focus on the sections of the paediatric population most likely to benefit from their efforts.

2.13. 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?

The requirements of the paediatric regulation have increased the overall number of patients being enrolled in clinical trials, although this might not always be seen at the member state level, given the multinational nature of many of these clinical trial programmes. Certainly, there have been several clinical trial applications received at the HPRA which have had an associated paediatric development plan. Interactions between the PDCO and developers appear to have clarified many of the important development issues prior to discussion at the Member State Level. This has improved the overall quality of paediatric clinical development, as it has resulted in greater expertise being applied to the initial assessment of the development plan, expertise which might not always be available at the individual member state level.

As regards any difficulties which might be experienced by developers, this has not been apparent from interactions between these developers and the HPRA. Many conversations between potential applicants and the HPRA relate to the classification of trials (often in adult subjects) as being interventional or non-interventional, which is outside the scope of the regulation.

2.14. 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?

From a regulatory perspective considerable resources are expended across the regulatory system in ensuring that the paediatric regulation functions correctly. These relate to procedures involving both new and historical paediatric clinical trials. These are assessed both as normal clinical trial application procedures, for which a fee waiver applies if the applicant is an investigator-sponsor, and also through Article 45 and 46 procedures for historical and new paediatric trial results assessment respectively.

New paediatric investigation plan (PIP) assessments and modifications to existing PIPs are also assessed at the Member State level. These assessments can be quite time-consuming, depending on the complexity of the individual procedure. The regulation states that applicants can avail of these procedures without incurring any fees, which is part of the incentives to facilitate paediatric development contained within the regulation. In addition, applicants may also avail of fee-waived scientific advice procedures for paediatric questions.

There have been efforts at the Community level to determine the resources being used at Member State level as part of all these procedures and the results of these are awaited. It may be that the results might have a bearing on the question of fees or other financial supports perhaps from the community as a whole.

2.15. Positive impact on paediatric research in Europe

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

It is apparent that, since the introduction of the paediatric regulation there has been an increase in the amount of paediatric research activity in Ireland, as evidenced by the various paediatric research networks which have been established. It is uncertain whether this is a consequence of the regulation itself, or as a result of a changes in paediatricians' interest in collaborative clinical research.

2.16. "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?

There is an emerging trend towards earlier access to new medicines, mediated in part through early access programmes at the various regulatory authorities (such as the EMA's PRIME programme). Whilst early access facilitation can have merits, there are potential risks within this trend to the appropriate development of paediatric medicines, as described in previous comments.

Currently, apart from the rewards and positive incentives contained within the regulation, the main penalty faced by developers is that their marketing authorisation application in adults may be delayed should they fail to engage appropriately with the requirements of the regulation with regards to parallel paediatric development. If earlier access to the authorisation step reduces the impact of this penalty, this might have the unintended consequence of reducing the incentive of conducting well-designed paediatric research, as the greater reward of the adult authorisation is more accessible. It also makes it more difficult to ensure that appropriate paediatric developments take place, as the medicine is available, so reducing parental perception of the need for participating in the appropriate clinical trials, as described previously.

Close collaboration between the various arms of the regulatory and reimbursement systems is essential to ensure that vulnerable groups are not adversely (albeit unintentionally) impacted by the desire to promote earlier access to medicines by other, less vulnerable groups.

2.17. Other issues to be considered

Consultation item No 17: Overall, does the Regulation's implementation reflect your initial understanding/expectations of this piece of legislation? If not, please explain. Are there any other issues to be considered?

The paediatric regulation has been in force for 10 years. In that time, significant advances have been made in the development, authorisation and availability of age-appropriate medicines for children, which would probably not have occurred in the absence of the legislation.

There are still some areas which have not worked as well as might have been expected. These relate mainly to the operation of the waiver and deferral systems within the regulation, as outlined above. In addition, the regulation has not delivered the results which might have been expected in the facilitation of paediatric

information to be added to older medicines which, although commonly used in children, have little sound scientific proof for such use.