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: **aPODD Foundation**

Transparency Register ID number (for organisations): **827378825872-78**

Country: **United Kingdom**

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aPODD Foundation is a non-profit organisation with the mission to accelerate the development of new medicines that are more effective and safer for the treatment of cancer in children. aPODD team is made up of parents, paediatric oncologists and drug development experts and the organisation is actively involved in drug repurposing initiatives and drug development collaborations with industry, academia and other charities. aPODD is a registered charity in England and Wales (1151744).

www.apoddfoundation.org

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

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Please indicate the level at which your organisation is active:

- Local
- National
- Across several countries
- EU

X 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?

In principle, specific legislation is useful to create a framework for developing medicines for children and ensure that certain criteria are met. Companies have now a clear path to follow for the development of paediatric medicines.

However, we think that one of the key objectives of the paediatric medicine regulation was to promote the faster development of effective and safe new medicines for children. This is particularly relevant for all the paediatric areas where children's diseases are different from adult ones, such as oncology. Since the enactment of the legislation, only two innovative medicines have been approved in Europe to treat specifically a form of paediatric cancer (Everolimus for SEGA in 2011 and Dinutuximab for NB in 2015). Most of the paediatric oncology drug approvals (9 in total) were for drugs already in clinical use and were not the direct result of legislation.
In keeping with the conclusion of the International Society of Paediatric Oncology in Europe (SIOPE) we think that the legislation did not have a significant impact for the development of new agents for children with cancer.

While it is important to stress the importance of evidence-based paediatric medicine, we must bear in mind that even before the paediatric legislation investigators sponsored trials had been conducted to ensure that drugs had been clinically evaluated in children with cancer and that the best possible treatments were proposed to sick children.
It is fair to say that all drugs used in children had been somehow clinically validated.

Nowadays, most children with originally metastatic diseases that do not respond and/or relapse after conventional therapy are left with only palliative therapies. What we need now is access to more innovative medicines and the legislation in its current form has so far had a negligible impact in paediatric oncology

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 legislation had undoubtedly a positive effect in all those therapeutic area where there is an overlap between the adult and the paediatric conditions. Drug development continues to be driven by the adult indications, as these are the main markets for the pharmaceutical industry.

This overlap is very thin in oncology since the cancers more frequently occurring in children and adolescents are different from those seen in adulthood.
Because of these differences companies can be granted waivers on the ground that the cancer does not occur in younger patients and thus skip the requirement to conduct paediatric studies, even when there might be a scientific/medical rationale for this (e.g. same mechanism of action of drug in both adult and paediatric diseases)

We do not agree with the statement that legislation can hardly influence this process. Legislation can indeed have a very powerful effect whenever strong incentives are introduced. The example of orphan drug legislation initiatives in both EU and US is a clear example of how proper legislative incentives and simplification can stimulate drug development for previously neglected diseases.

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?

As stated above, the legislation did not have a significant impact on the approval of new agents for children with cancer. Therefore we do not have evidence of new licensed treatments replacing older ones.
Moreover, the few new treatments approved so far are mainly used for children in relapse or patients that have run out of options. What we would need more urgently is also more effective front line therapies.

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?

The costs imposed are not trivial. They may be sustainable for larger pharmaceutical companies but they are often burdensome for smaller biotech companies. For example we have direct evidence of companies even willing to consider voluntary PIPs but lacking the resources for these. This situation

further support our call for better financial incentives to be offered to companies willing to develop specific drugs for paediatric cancers (to be detailed 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?

The current reward system has serious limitations. While we agree that a supplementary protection certificate (SPC) of 6 months has in theory substantial value, it does not create a powerful enough incentive for two main reasons.
Firstly, it comes too late. The reward is actually many years away, at the end drug's life cycle. This also makes it also more difficult to quantify the SPC value since companies are required to start paediatric studies before regulatory approval.
Secondly, it is strictly linked to adult compound development. The compound may be discontinued during adult clinical studies thus eliminating the potential reward for paediatric development.

We strongly support a review and improvement of this reward system. We strongly believe that innovation cannot be mandated with stronger obligations. This approach would have only a very limited impact. We can unleash innovation only when we can create a fertile ecosystem with compelling incentives.

Our idea is that reward must come earlier and must be equally attractive for both larger pharmaceutical companies and smaller biotechs. A fully transferable SPC modelled on the priority review voucher system in the US could be a move in the right direction.

2.6. The orphan reward

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

Incentives provided by Orphan Drug Legislations (both in EU and US) have not had a significant impact on paediatric oncology drug development, even though they did for many other rare diseases. From an industry perspective this is not surprising as there are some features of childhood cancers that make it more challenging. Some are more scientific, other are more financially related

Pharmaceutical and biotech companies have been focusing on rare diseases that have some very specific genetic defects (e.g. Cystic Fibrosis, Duchenne Muscular Distrophy), which tend to make drug development work more straightforward as opposed to cancer, which is a systemic disease with multiple pathways involved and has a higher failure rate.

Secondly, specific paediatric oncology drugs tend to have smaller financial returns, even when compared with equally rare diseases. Many rare diseases have similar incidence as childhood cancers but they tend to build up progressively. As a results at any given time there are higher patient numbers. In purely financial terms the rewards are expected to be higher for these rare diseases, for which higher reimbursement prices can often be negotiated. It is unlikely that in the case of childhood cancer premium prices can be applied if the same drug is also used in adult cancer.

In terms of extra SPC reward for orphan designation (2 years as opposed to 6 months) the difference has not made any difference. The key problem is that the development is still driven by the adult disease. If the adult cancer is rare, it is also possible that it will not be seen in children and adolescents, thereby creating the conditions for a waiver.

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?

We think that there are still problems related to implementation. One key challenge is the timing of the paediatric investigation plans. According to the regulation these should be submitted to EMA "at the end of pharmacokinetic studies in adults", which should generally correspond to the end of Phase I. This rarely happens as companies tend to delay this process as much as possible. Currently there is no formal penalty in place for this delay, the only requirement being that companies have to get a PIP approved before MA.

According to industry, it is difficult to present a PIP at a very early stage of development when limited clinical data are available. This is a reasonable concern in our opinion.
Perhaps one solution would be to introduce the concept of a "staged" PIP, where companies would initially be requested to submit a plan covering only the early development stages (e.g. pre-clinical and Phase I) followed by a follow up plan once more data become available from adult studies and the initial paediatric studies.

In relation to waivers, we are aware that EMA revised the class waiver list in 2015, shortening the list of diseases for which companies could request a waiver. However, this modification is unlikely to change dramatically the drug development prospects for children with cancer. If the relevant disease does not occur in children, the company may still obtain a waiver even though there might be a scientific rationale for paediatric development on the basis of a common mechanism of action

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?

We are overall in agreement with the principle that a waiver should be awarded whenever the disease does not occur in children or the clinical studies would not be recommended for other reasons.

This approach, however, creates a problem in paediatric oncology.
Cancers occurring in children are biologically different from those occurring in adults but in some cases they may share some specific disease-related molecular pathways. For this reasons compounds that are being developed for adult indications may well be efficacious in certain childhood cancers. Failing to take into account the medicines' mechanism of action and focusing instead only on the tissue of origin creates missed opportunities for sick children.

The best example of a missed opportunity under the current legislation is given by Crizotinib, an

ALK inhibitor that was originally developed to treat non-small cell lung cancer (NSCLC). This drug was originally granted a waiver in EU, even though the same actionable mutation was known to be present in a subset of neuroblastoma patients. Studies were subsequently started in the US, which showed encouraging clinical activity in these patients. If the mechanism of action principle had been taken into account on this occasion, European children may have had access to this therapeutic option much earlier.

On the basis of data provided by EMA over 60% of 89 potentially valuable anticancer drugs were granted a waiver. Only 9% to 15% of all oncology agents in development have ongoing paediatric studies. The introduction of new targeted agents in paediatric oncology is not only promising for the possible reduction of chemotherapy-related toxicity but also because there is hope that they may even deliver more benefits to younger patients, compared with adults. In fact it has been shown that the average number of mutations in childhood malignancies is on average about 100-fold lower than in adult tumours. This observation suggest a much more promising target population for mechanism of action- based drug development.

2.9. Deferrals

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

We are in agreement with the idea that deferrals should be granted to ensure that clinical studies are performed only when it is safe and ethical for children. We also agree that there is no evidence that the paediatric regulation has delayed adult drug development.

The reality is that children get access to potentially life-saving drugs much later than they should because the current system let companies delay paediatric studies, even when there is no strong scientific rationale for this and commercial considerations only may explain this delay. We need to bear in mind that, while safety is important, children with cancer are facing life threatening diseases and most children with metastatic diseases that relapse after front-line therapy are left without any therapeutic alternative.

At the moment, the regulation does not envisage penalties for companies that unnecessarily delay paediatric studies. Moreover, the current regulation may unintentionally cause also delays because of the requirement to present a complete development plan at the end of pharmacokinetic studies in adult. This is often too challenging a task and many companies may be tempted to request a deferral.
If a staged-PIP approach were to be introduced, it is possible that more studies will be initiated at the appropriate time.

2.10. Voluntary paediatric investigation plans

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

There are currently very weak incentives in place to support voluntary PIPs, even though EMA encourages this approach and indeed offers free scientific advice. We only have a few examples of companies pursuing this approach. These are either big pharmaceutical companies, which rich development pipelines and strong internal resources or, possibly, smaller biotech companies that

collaborated with academia and received support from other, non-profit funding sources (e.g. EU grants, charities and foundations).

We cannot force innovation through tougher regulations and obligations. We can only make innovation possible by creating the right environment and incentives to overcome the financial and operational challenges of paediatric oncology drug development.

We believed that US initiatives such as the priority review voucher for rare paediatric diseases approval are a step in the right direction. An applicable solution in EU could be a transferable supplementary protection certificate to be awarded upon regulatory approval of agents that were specifically developed for a childhood cancer indication and, possibly, upon completion of voluntary PIPs if that generated data support paediatric use.

2.11. Biosimilars

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

We do not have specific comments for this section. It is probably too early to judge the impact of biosimilars in paediatric oncology

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?

We agree that the PUMA concept is a disappointment. It is clear that the provided incentives are not sufficiently strong and cannot overcome the operational and financial challenges. The success of PUMA appears to be crucially dependent upon the development of a paediatric drug formulation that may offset off-label use of the generic versions in clinical use. There are also some open questions regarding the feasibility of premium pricing and acceptance of this by the national payers.

This outcome is truly disappointing as there is a lot of valuable paediatric data available within industry and academia, which could be exploited in a cost-effective manner to benefit patients.

We are very supportive of drug repurposing initiatives and we would welcome a multi-stakeholder discussion on how we could modify the PUMA concept in order to make it more attractive for companies to re-purpose drugs for paediatric diseases.

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?

It is certainly the case in paediatric oncology that significantly smaller number of patients are available for clinical studies, compared with more common adult diseases. This limitation, common to all rare diseases, calls for more extensive use of in silico modelling and innovative clinical trials approaches.

The Paediatric Regulation has certainly encouraged the use of novel methodologies. However, this support has not yet produced dramatic effects

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?

Free of charge assessment of paediatric plans certainly facilitates early interactions and the exchange of information with regulators. On the other hand, it is fair that the professionals involved get some form of compensation for their work. We would expect national regulatory agencies or other national public bodies to enable appropriate compensation for the paediatric specialists involved in these discussions with drug developers.

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?

The Paediatric Regulation has undoubtedly stimulated paediatric research and increased awareness within industry and academia. Moreover, it has certainly stimulated dialogue among all key stakeholders. The creation of the ACCELERATE platform for paediatric oncology drug development is probably the most tangible example.

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?

We would expect that emerging "omics" technologies and molecular profiling would further push the industry towards precision medicine approaches, which at some point may call for novel trial design and certainly change the legislation to include the principle of mechanism of action into a revised paediatric regulation.

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?

These would be our key suggestions:

- The legislation does not address the drug development needs of certain therapeutic areas, whereas others tend to be overrepresented in PIPs. We urgently need better rewards that may create stronger incentives, particularly for smaller pharmaceutical companies and biotechs.
- More flexible entry criteria for adult oncology trials to enable adolescents to enter these trials whenever paediatric studies are simply not feasible. This would require changes in other areas but would probably also demand modifications to the existing paediatric legislation, which currently group adolescents with children
- PIPs have to be submitted at a very early stage of human development, leading to unnecessary delays caused by numerous modifications. Any modification that would make this process more flexible would be very beneficial (e.g. "staged" PIPs)
- Harmonization of FDA and EMA paediatric plan requirements would be extremely beneficial and would clearly facilitate the regulatory approval process. Harmonization of PIP/PSP would probably save time and resources
- In keeping with the point above, we should work together to create stronger, well trained paediatric networks and facilitate international collaborations.