# 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: **Zoé4life**

Transparency Register ID number (for organisations):

Country: **Switzerland**

E-mail address: **nicole@zoe4life.org**

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

- X **My contribution may be published under the name indicated; I declare that none of it is subject to copyright restrictions that prevent publication**
- ○ My contribution may be published but should be kept anonymous; I declare that none of it is subject to copyright restrictions that prevent publication
- ○ I do not agree that my contribution will be published at all

### Please indicate whether you are replying as:

- ○ A citizen
- ○ A business
- X **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
- X **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?

We agree that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines. The Paediatric Medicines Regulation has been an important step in stimulating research and development into therapies for children. However, it has had limited impact in childhood cancer. Only 2 new drugs specific to paediatric oncology: Votubia and Unituxin have been approved through a Paediatric Investigation Plan.

*(Ref:Vassal G. (2016). Accelerating new oncology drug development for children and adolescents: challenges and the European Strategy. Unpublished paper presented at 48th Congress of Paediatric Oncology, 19 - 22 October, Dublin)*

In Europe, more that 50% of drugs given to children have never been investigated in this population, but only in adults and not necessarily for the same disease. These medicines are therefore administered "off-label".

*(Ref: ITCC (2016) Why is a New Regulation Necessary?*
*Accessed 26 / 11/ 16 at: http://www.itcc-consortium.org/new-regulation-necessary.php)*

Paediatric cancers are rare – as there are few cases and limited profits, pharmaceutical companies have no interest in this drug development.

Legislation is therefore required to guarantee development of evidence-based paediatric oncology medicines – and a re-evaluation and modification of the current legislation is necessary

### 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 Regulation so far has not contributed significantly to the availability of important new treatment options for childhood cancer. This is mostly because the regulation considers only drugs developed in adults and in the situation where the condition is the same in children and adults. Most childhood cancers are different than adult cancers.
This situation is influenced by the legislation. Since waivers can be granted on the ground that the disease does not occur in children, the legislation is directly responsible for several scientifically and medically unjustified waivers of anticancer drugs, which could have been effective in children.

We therefore do not agree with the Commission's findings that this is "partly dependant on factors that can hardly be influenced by legislation."
We strongly feel that paediatric oncology urgently needs a regulatory change to improve the situation of children with cancer.

## 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?

We believe there has been no significant increase in medicines for childhood cancer. Pharmaceutical companies can apply for a waiver or a deferral if the adult illness does not exist in children, but the fact is that children are not affected by most adult cancers.
However, the mechanism of action of an adult drug can benefit a paediatric cancer. On example of this is crizotinib, a lung cancer drug, which was granted a waiver and yet proved to have a positive impact on some childhood cancers. We feel that it is this failure to recognise that the mechanism of action of a drug should be the main factor in establishing a Paediatric Investigation Plan (PIP) that has resulted in numerous lost opportunities.

Most waivers to the obligation to conduct PIPs were granted in the field of oncology. However, 63% of the drugs which were waived were relevant for paediatric malignancies.
As a result, many potentially active oncology drugs have not been investigated.
Specifically:

- 214 class waivers were discussed,
- 72% for an oncology drug, from which 95% were granted waivers (147 drugs)

63% of the drugs waived were relevant to paediatric malignancies and more data was needed for 17% of them. In other words, about 70 % of waivers in the field of oncology were granted without scientific valid grounds.

*(Ref: Vassal G. (2016). Accelerating new oncology drug development for children and adolescents: challenges and the European Strategy. Unpublished paper presented at 48th Congress of Paediatric Oncology, 19 - 22 October, Dublin)*

## 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?

We have no specific comment regarding the costs for pharmaceutical companies to comply with a paediatric investigation plan. It is with interest that we note SIOPE's point that the average cost of a PIP is 20 million euros, which is far less than the cost associated with adult development.
We support Unite2Cure's proposal that changes to the reward system would create better incentives for industry.

## 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?

Most Paediatric Investigation Plans in oncology are either waived or significantly delayed. It seems clear that the balance between the cost of an oncology PIP and the possible reward is not sufficiently attractive to the pharmaceutical industry. Furthermore, the failure of a drug to show positive results in an adult cancer has led to cancellation of the corresponding PIPs, even though there may be scientific evidence of the potential for benefit for children.

Incentives are needed that:

- reward investment in paediatric cancer drugs development proportionately
- offer these rewards sooner
- stimulate paediatric investigations uncoupled to those for adult cancers
- reward paediatric oncology drug development in collaboration with cooperative/academic groups

## 2.6. The orphan reward

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

Every different type of cancer in children is a rare disease, and all paediatric cancers together fall within the definition of a rare disease. However, the orphan drug regulation did not impact the development of new oncology medicines in children before the paediatric regulation was in place and also has not since then.

## 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 do not feel that there have been significant improvements in the implementation of the regulation for childhood cancer. We recognize that in 2015 some class waivers which had allowed companies to avoid the requirement to file a PIP were revised. However, these measures will only come into effect in 2018.
The removal of some of the broad class waivers should lead to more research in paediatric oncology. However, drug companies could still apply for "product specific waivers". In fact, if a company requests a waiver because the disease does not exist in children, even though the drug's mechanism of action is relevant for paediatric malignancies, the EMA cannot force the company to file a PIP.

## 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?

Although the Regulation has brought positive change and advances, the possibility to apply for and receive a waiver has resulted in many lost opportunities. In fact, over 60% of 89 potentially valuable anticancer drugs were granted a waiver, there are still few paediatric trials and only between 9% and 15% of all oncology agents have ongoing paediatric studies.

*(Ref: Pearson et al. (2016) Implementation of mechanism of action biology-driven early drug development for children with cancer, European Journal of Cancer, Volume 62, July 2016, Pages 124–131. Accessed 2.01.17 at: http://www.sciencedirect.com/science/article/pii/S0959804916320597*

Crizotinib is one example of this. This drug was authorised in Europe for treatment of non-small cell lung cancer (NSCLC), an adult cancer. Despite being known to be active at a molecular level in childhood cancers, including lymphoma, the PIP was waived in 2010 on the grounds that "NSCLC does not exist in children". The benefits of this drug were later confirmed thanks to trials conducted in the United States.

(*Ref: ITCC. (2012.) General report on experience acquired as a result of the application of the Paediatric Regulation. Viewed 18/07/15 at: http://ec.europa.eu/health/files/paediatrics/2013_pc_paediatrics/31-itcc.pdf)*

## 2.9. Deferrals

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

We agree that there is no evidence that the paediatric requirements have delayed the processing of adult applications.
Delays with paediatric plans are, however, a major issue in our opinion. Specifically, those for oncology, which are unlikely to be submitted at the end of the phase 1 trial in adults, despite this being a legal requirement and which are in many cases granted a deferral. The result is that drug development in paediatric oncology is significantly delayed compared to adults.
We share the frustration mentioned in the report "where the treatment for a life-threatening disease will only be available to children years after the adult authorisation."
We are also concerned that deferrals may ultimately lead to PIPs becoming unenforceable, because once the marketing authorisation for adults is granted, deferred paediatric studies may be delayed or not initiated at all. The most significant deterrent of the Regulation is non-validation of the marketing authorisation application but once the product becomes authorised this is not applicable. This means there are no ways to enforce the PIP once the product is authorised. Furthermore, once the medicine is authorised in adults and therefore available for off-label use in children, it becomes more difficult to recruit children into clinical trials.
We are concerned that there is no penalty for submitting a PIP late.

### 2.10. Voluntary paediatric investigation plans

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

There have been insufficient voluntary PIPs to provide any significant benefits for children with cancer.

The 10 year report by the EMA states:

"Experience from the EU, the US and other regions conclusively shows that a system based exclusively or primarily on voluntary initiatives from developers, or solely on incentives, does not result in development of medicines that address satisfactorily the public health needs of children….

Between 2011 and 2014, the Agency confirmed the applicability of the class waiver in 73 cases and identified a potential paediatric interest for 50 of them (68%). Unfortunately, the suggestion to submit a PIP application to cover a new paediatric development was accepted only in a single case, suggesting that rewards without obligations have some limitations in fostering the development of paediatric medicines".

We feel that our children's lives should not depend on the goodwill of the pharmaceutical industry. Adequate research into childhood cancers should be a requirement.

### 2.11. Biosimilars

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

Since there are few biological agents developed for children, we do not think that biosimilars would have an impact on childhood cancer drug development.

### 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 is a disappointment, since only 2 PUMAs have been granted in 10 years. It did not work in paediatric oncology.

### 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?

Paediatric developments by pharmaceutical companies should be done systematically in collaboration with cooperative groups and networks, including early interaction to best design PIPs with regards to needs and feasibility.

Regarding the ethics of conducting clinical trials on children, we feel that children have a role in determining their own lives and should be seen as active participants in research. The assumption that all children are necessarily vulnerable may prevent worthwhile research from going ahead.

### 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?

No comment

### 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?

In the field of paediatric oncology, the regulation did not change clinical research since the community has been running academic clinical trials for over 50 years.
We do agree however that the regulation has increased the interactions between pharmaceutical companies and the paediatric oncology community.
Furthermore, the collaboration between parents and paediatric oncologist networks has been instrumental in discussing and working out the limitations as well as the positive points of the regulation as well as proposing solutions to accelerate new drug development for children with cancer.
We feel that overall, although the PMR did change the landscape in in paediatric oncology, it is far from addressing the needs of children with cancer.

### 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?

Precision medicine, molecular profiling, and other emerging trends have the potential to have a major impact and offer considerable hope for children and their families.
Making mechanism of action intrinsic to the Regulation will add an impetus to these exciting new developments.

### 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?

We support the recommendations in the Position Statement by SIOPE, Unite2cure and Cancer Research UK:

-Ensure that the obligation to undertake a Paediatric Investigation Plan is based on how a drug works and its capacity to address an unmet medical need in children - rather than the type of disease in adults for which it is first introduced.
-Reduce delays in paediatric medicines reaching children by enabling Paediatric Investigation Plans to start not later than the start of pivotal trials in adults, if paediatric biological, preclinical and preliminary clinical data are available to better evaluate the potential therapeutic benefit in the paediatric population.
-Set up a mechanism to choose the best potential drugs and prioritise, among drugs developed by different companies, in relation to the real needs of children affected by rare cancers.
-Add provisions for more effective and flexible rewards for companies undertaking early and timely Paediatric Investigation Plans and those researching therapies specifically for cancers which only occur in children.

Furthermore, we would like changes to the rules regarding access to trials for adolescents. There is no medically or regulatory reason to exclude adolescents from adult trials - this is just a question of change of attitude and mind-set.