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:  CCI-Europe (European Regional Committee of Childhood Cancer International)

Transparency Register ID number (for organisations):

Country: Europe

E-mail addresses: oesterreichische@kinderkrebshilfe.at and nicole@scobie.ch

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
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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
- National
  - **X** Across several countries
    - EU
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.

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”.

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.

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 have been no significant increase in medicines for childhood cancer. Pharmaceutical companies can apply for a waiver or a deferral if the adult illnesses does not exist in children while children are not affected by most adult cancers. The mechanism of action of an adult drug can benefit a paediatric cancer; for example, crizotinib, a lung cancer drug, was granted a waiver and yet proved to have positive impact on many childhood cancers. Failure to recognise that the Mechanism of Action of a drug should be the main factor in establishing a Paediatric Investigation Plan (PIP) has resulted in numerous lost opportunities.

Most waivers to the obligation to PIPs were granted in the field of oncology. However, many of those drugs are relevant for paediatric malignancies. As a result, many potentially active oncology drugs have not been investigated.
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 comment regarding the costs for pharmaceutical companies to comply with an agreed paediatric investigation plan but we note with interest that the average cost of a PIP is 20 Million Euros, far less than the development in adults.

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?

We believe that it is the requirement to submit a PIP as an obligation before filing in adults that is the strongest determinant for pharmaceutical companies to design and run PIPs, and not the possibility of a reward.
We feel that the way the reward system works at present only creates the incentive to comply with the requirement as late as possible.
We therefore feel that a better reward system should be put in place. There should be better incentives to reward companies willing to address paediatric needs through research and development, rather than complying with a regulation late.
2.6. The orphan reward

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

The Orphan Drug Legislation did not deliver on its promises in the field of paediatric oncology despite the fact that each paediatric cancer is a rare disease. The Orphan Drug Legislation reward is not sufficiently attractive to mobilise research in the field of paediatric oncology. Therefore, the orphan reward has not had any impact on the development of new paediatric anticancer drugs.

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 has been any improvement of the implementation of the Regulation over time, with regards to paediatric oncology. The PIP process is too long and too complex. The EMA and PDCO can not force any paediatric development even if it medically and scientifically justified.
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 agree with the European Medicines Agency’s conclusion in its 10 year-report to the Commission (p. 56) about the importance of the Mechanism of Action principle:
Paediatric oncology has been identified as a neglected therapeutic area as little progress has been made with new and better treatments for childhood cancers, and this was attributed in part to the difference in clinical conditions between adults and children. Cancers that concern children are biologically different from those concerning adults, and therefore any medicine's mechanism of action needs to be used to guide investigating treatments of the paediatric malignancies and to address the unmet therapeutic needs in paediatric oncology. Consequently, the development should be driven by the potential paediatric use, i.e. by the data (existing or to be generated as part of a PIP) on the mechanism of action, or on the target of the anti-cancer medicine where the anti-cancer adult indication is under development.

One example of how opportunities are missed under current system is that of the drug Crizotinib. This drug was authorised in Europe for treatment of non-small cell lung cancer, an adult cancer. Despite being known to be active at a molecular level in childhood cancers, including lymphoma, the PIP on crizotinib was waived in 2010 on the grounds that “NSCLC does not exist in children”.
2.9. Deferrals

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

We agree that deferrals for any other reason than safety are delaying the start of trials, access to innovation and this is of major concern in the situation of life-threatening diseases such as childhood cancer.

2.10. Voluntary paediatric investigation plans

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

We agree that there is no evidence that the paediatric requirements have delayed the processing of adult applications. However, delays with oncology PIPs where drug development is significantly delayed compared to that for adults are a matter of major concern as this is a life-threatening situation. We are frustrated that, as the Commission states, treatment ‘for a life-threatening disease will only be available to children years after the adult authorisation’.
2.11. Biosimilars

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

No comment

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 feel that the PUMA concept is a disappointment since only 2 PUMAs have been granted in 10 years. It clearly 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?

We need more drugs, earlier and for more children. Therefore, more clinical trials are needed. In regards to the ethics of conducting clinical trials on children, we feel that children should be seen as active participants in research since they have a role in determining their own lives. It should not be automatically assumed that all children are vulnerable as this 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?

We feel that the Regulation has had an impact in terms of attitudes and awareness within the industry and amongst academic researchers, and in the establishment of collaborative networks, ACCELERATE being one example. However, this has not been reflected in actual results for childhood cancers.

Childhood cancers still remain the first cause of death by disease for children in Europe.

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?

Emerging developments, such as precision medicine and molecular profiling, should have a major impact on the development of paediatric medicines and the relevance of the Paediatric Regulation. It is important that the Regulation be adapted to make the mechanism of action principle an essential feature in the development of these future medicines.
### 2.17. Other issues to be considered

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<th>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?</th>
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We support the recommendations in the Position Statement by SIOPE, Unite2cure and Cancer Research UK:

1. 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.

2. 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.

3. Reduce delays in paediatric medicines reaching children by enabling Paediatric Investigation Plans to be submitted 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.

4. 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.

To this, we would add a further item:

Introduce flexible ages of entry to adult trials based on considerations of biology and safety.