

# 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: The European Consortium for Innovative Therapies for Children with Cancer (ITCC)

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

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- Local
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- 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?

ITCC, a network of 51 centres carrying out clinical investigations and 22 paediatric cancer research laboratories in 12 EU countries and Israel, was created in 2003 to anticipate the Paediatric Regulation and establish in Europe the capacity to run early oncology drug trials and translational research, in partnership with pharmaceutical companies. ITCC was thus an academic initiative to anticipate the need for a strong EU academic structure and programme to implement the Paediatric Regulation and meet patients' needs.

The Paediatric Regulation has had a positive impact on the field of paediatric oncology drug development. In 2003, there was only one ITCC phase II trial with an innovative compound (Glivec™ in paediatric solid tumours). In 2016, the ITCC portfolio contained 21 phase I and II trials with innovative compounds as single agents or in combination. A clear shift was observed, due to the Regulation, starting in 2008-2009.

However, the needs of children have not yet been addressed: 6000 young people still die of cancer each year and only 10% of children and adolescents with a life-threatening relapsed malignancy have access to an innovative treatment at a time there is an outstanding acceleration in oncology drug development in adults with more active compounds than ever being available.

ITCC agrees that specific legislation is required to support and accelerate the development of new effective medicines for children with cancer. But **there is an urgent need to modify the Regulation and improve its implementation**, based on experience gained over the last 10 years. ITCC proposals will be made in the following pages.

### 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?

New drugs for the treatment of paediatric leukaemias have been developed and new treatment options, such as nilotinib, dasatinib, blinatumomab are available. Most of the time those drugs address diseases occurring both in adults and children.

In contrast, only two drugs have been approved for malignancies in solid tumours through a PIP, namely Votubia™ (mTOR inhibitor for sub-ependymal giant cell astrocytoma) and Unituxin™ (anti-GD2 monoclonal antibody for neuroblastoma).

Two issues have been clearly identified in paediatric oncology:

- drugs have been unjustifiably class-waived (from a scientific and medical standpoint) because the adult condition does not exist in children
- paediatric oncology developments have started too late; only a few months before first authorisation in adults or even after the drug is marketed

ITCC calls for :

**1. Mechanism-of-action based PIPs and paediatric development of drugs based on scientific data:**

**2. Early start of paediatric developments as already requested by the Regulation**

### **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?

The number of new paediatric medicines available and authorised for the treatment of paediatric malignant solid tumours and leukaemia has not substantially increased, while between 2011 and 2015<sup>1</sup>, 70 new oncology medicines have been authorised and launched for the treatment of adult cancers .

This is of major concern for a disease being the leading cause of death by disease beyond one year of age.

<sup>1</sup> IMS institute of Health informatics, December 2015

### **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?

ITCC has no comment regarding the costs for pharmaceutical companies, but we note with

interest that the average cost of a PIP is 20 M€, far less than the development of a drug 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?

ITCC understood that having a positive compliance check of trials in PIPs was not enough to get a reward since a company needs to submit in each member state to get a SPC extension. It is obvious that over the last 10 years, the obligation of submitting a PIP was a major driver rather than getting a reward.

Under the current system the only time limit to run a PIP is thus the duration of SPC and the probability to complete a PIP in due time. It is not an incentive to start early paediatric developments.

There is no reward to incentivize early submission and starting of PIPs as requested by the regulation.

ITCC believes that the reward system should be modified to really reward those companies considering paediatric oncology drug development as a science driven R&D activity with the need to start as soon as possible rather than only a regulatory obligation to comply with.

In addition:

- There is no reward to incentivize paediatric oncology drug development against specific paediatric targets that would lead to a first marketing authorization in a paediatric condition.
- There is no incentive to continue the paediatric development of a drug (when relevant) if its adult development is stopped, for any reason.

**The reward system needs to be modified to better incentivize paediatric oncology drug development run in a timely fashion** that will give the same pace as adult oncology drug development, currently.

## 2.6. The orphan reward

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

To determine how the orphan drug regulation incentivized paediatric oncology drug development since 2000, ITCC analysed the 657 European Orphan Drug Designations (ODD) and 46 authorised orphan oncology drugs over the last 16 years. The results are currently submitted for publication.

The Orphan Drug Regulation failed to promote the development of innovative therapies for malignancies occurring specifically in children with only 2% of ODDs related to paediatric cancer and many paediatric malignancies having no medicines with an ODD. Only 2 new anticancer drugs have been approved with an innovative mechanism of action.

For orphan drugs intended to treat rare malignancies occurring both in adults and children, paediatric drug development started late (and some have not yet commenced) as compared to adult development and was driven by the obligation of the Paediatric Medicines Regulation rather than the attractiveness of incentives provided by the Orphan Drug Regulation.

Thus, **the Orphan Drug Regulation did not facilitate the development of new anticancer medicines for children**, both before the Paediatric Regulation was in place and since it has become operational.

There is a need to set up a system to reward and incentivise development of oncology drugs which will be specific for paediatric malignancies and first marketed in children. The successful US Priority Review Voucher illustrates that such types of reward are able to accelerate and incentivise paediatric drug development.

## 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?

ITCC agrees that the implementation has improved overtime as it is obvious when we compare activity in 2008 and 2016. There was a learning curve for each stakeholder, but it does not mean that the situation is now optimal and that there is no need to significantly improve the regulatory environment.

To illustrate the issues, ITCC wants to highlight one example.

Nivolumab (Opdivo™), a check point inhibitor, is highly active in Hodgkin's lymphoma, a disease occurring in adults, adolescents and children. Marketed authorisation in adults was granted in the US in May 2016 and is likely to be granted in EU very soon. The current Summary of product characteristics states that: "*the safety and effectiveness of Opdivo™ have not been established in paediatric patients*". Indeed, a PIP for Hodgkin's lymphoma was granted in EU in February 2016 and the trial has only recently started. Access for children and adolescents to an effective drug has been delayed by 3 to 4 years, and the paediatric trial started when the drug is already authorized in adults. Off label use is likely to impact accrual in the paediatric trial.

For improvement, ITCC calls for:

- 1. Simplify and shorten evaluation of PIPs by EMA**
- 2. Implement systematically mechanism-of-action based PIPs**
- 3. Reinforcement of early submission of plans**
- 4. Make PIPs content publically available, as this is mainly a non-competitive field**
- 5. Establish priorities among drugs by disease to increase feasibility and likelihood of efficacy**

## **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?

ITCC analysed class-waivers granted by the EMA since the launch of the regulation. The results are currently submitted for publication. 64% of all class waivers concerned an oncology product. This highlights that: a) there have been many oncology drugs developed over the last 10 years, and b) most adult cancers, such as breast, lung, prostate and colon cancers, do not occur in children. The study showed that:

- 70% of class-waived oncology drugs were considered relevant for paediatric malignancies on the basis of information related to their mechanism of action, ie the class waiver was not scientifically relevant
- 27% required more information (biological and preclinical) to define the relevance to paediatric malignancies, ie the decision was not well informed
- 3% were not relevant, ie the class waiver was scientifically relevant.

This does not mean that all these drugs should have been studied in children, but it does mean there is a need to inform decisions more scientifically and to have the capacity to prioritise drugs when several drugs address the same targets. Oncology drugs will still need to be waived but it should be based on data and science rather than being centred on the condition in adults.

ITCC calls for:

- 1. Implementation of mechanism-of-action (MoA) driven PIPs and suppression of article 11 b: of the Paediatric Regulation**
- 2. Systematic biological and preclinical evaluation of drugs to define their relevance for paediatric malignancies, including comparison of compounds from several companies when they have similar MoA.**
- 3. Establishing priorities among drugs by disease to increase feasibility of PIP and likelihood of efficacy, ie better meet patients' needs.**

Those arguing that “changes to the waiver concept risk endangering the objective of disease-agnostic statutory rules as well as the predictability of paediatric investigation plan decisions with regard to the expected scope of paediatric research” are running the risk of overlooking the reality of the needs of children with cancer.

## 2.9. Deferrals

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

ITCC agrees that deferrals for any reason, other than safety and potential lack of efficacy over existing treatments (article 11/:a and 11/:b of the Paediatric Regulation), result in delaying the start of trials and access of patients to innovation. This is of particular and major concern in the situation of life-threatening diseases where time is an issue.

## 2.10. Voluntary paediatric investigation plans

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

There are clear successes of voluntary paediatric investigational plans outside the adult condition. Dabrafenib, a B-RAF inhibitor, is being successfully developed in B-RAF mutated paediatric malignancies, such as B-RAF mutated low or high grade gliomas in children with. Conversely, the development of vemurafenib, a B-RAF inhibitor, within the strict scope of the Paediatric Regulation (ie the adult condition), ie only in B-RAF mutated paediatric metastatic melanoma, failed.

If the development of effective new anti-cancer drugs rely on the willingness of a company to run a voluntary PIP, this is in conflict with the spirit of law: addressing paediatric needs through obligation and rewards.

In addition, the reward is the same for a company starting paediatric development late for the treatment of an adult disease occurring in children, as it is for another company starting a voluntary PIP for the treatment of a paediatric malignancy with high unmet medical need, early.

ITCC calls for:

- 1. MoA based paediatric plans along with prioritization among compounds of the same class**
- 2. Incremental rewards to better incentivize paediatric developments without delay and without deferral (unless medically justified).**

## 2.11. Biosimilars

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

In paediatric oncology, we are unfortunately not in the situation of having biosimilars of monoclonal antibodies approved for paediatric use, since we do not have monoclonal antibodies at the end of their patent.

## 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?

Almost all chemotherapy drugs used daily to treat children and adolescents with leukaemia and malignant solid tumours (overall disease free survival at 5 years is 80%) are off patent and 50% have no recommendation for paediatric use in their SmPC. However, their use, including dosing and pharmacokinetics, have been established and validated through published academic run trials. There is no need to conduct new studies to obtain a PUMA.

In paediatric oncology, we identified in 2007 that the needs for research on off-patent anticancer drugs that could fall under the PUMA concept were:

- o Age appropriate formulation of oral anticancer drugs
- o Dosing of chemotherapy below one year of age
- o Long term toxicity in childhood cancer survivors

ITCC believes research on these three topics should be funded through European grants

## 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?

ITCC runs phase I and early phase II trials in collaboration with the other SIOPE<sup>1</sup> clinical trial groups running late phase II and phase III trials in all paediatric malignancies. This provides the capacity to deliver a full paediatric investigation plan (from phase I to randomised phase III) through collaboration with cooperative groups with high quality research and expertise.

Partnering (ie before starting to design the PIP) with cooperative groups early is of major added value for pharmaceutical companies to assure that their PIPs will meet the needs of patients, will consider state of the art treatments, and will be feasible. We believe this is the only way to run efficient paediatric oncology drug development.



## 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?

Experts should be compensated for additional work performed outside of their daily job.

There is no reason why paediatric drug development should be cheaper.

## 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?

ITCC considers that the Paediatric Regulation has definitely changed the landscape of paediatric oncology drug development and encouraged the implementation of early phase clinical trials of new anti-cancer drugs.

Even though the paediatric oncology community has developed clinical research infrastructures to efficiently run trials and PIPs, there is a need for structures to fund projects to consolidate and expand the capacity to accelerate paediatric oncology drug development.

## 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 cancer medicine, ie generating tumour molecular information (including liquid biopsies), is now an integrated part of paediatric oncology drug development in Europe. ITCC is coordinating programmes such as MAPPYACTs and INFORM to generate comprehensive genomic tumour information for patients at relapse in order to drive therapeutic options through early trials. This will generate 1000 exomes in relapsed paediatric malignancies by 2019.

In addition, master protocols with several drugs from different companies, such as AcSé-ESMART and INFORM2, are running or in preparation to expand the number of drugs to be proposed and match tumour molecular alterations found in patients' tumour. These trials including new designs and methodology aim to accelerate innovation for patients and

should be considered as new options when paediatric development plans are discussed with regulatory agency.

ITCC believes that there is a **need for greater cooperation between academia, industry, regulatory bodies and parents** to innovate in paediatric oncology drug development and **accelerate the development of new and effective medicines and therapeutic strategies.**

The development of gene-modified cell therapies should be facilitate considering the borad field of applications for the treatment of paediatric malignancies

## 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 opinion of ITCC is that the following changes should occur to accelerate innovation for children and adolescents with cancer and meet their needs:

1. Ensure that the obligation to undertake a Paediatric Investigation Plan is based on how a drug works (mechanism of action) 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. 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. The availability of biological, pre-clinical and preliminary clinical data in children will enable the potential therapeutic benefit of a new drug in the paediatric population to be more accurately determined and inform a PIP.
3. 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.
4. Add provisions for more effective and flexible rewards for companies undertaking early and timely PIPs and those researching therapies specifically for cancers which only occur in children.
5. Set up new rewards to incentivise the development of specific paediatric drugs that will be first marketed in children and the repurposing of drugs whose adult development failed while they are scientifically and medically relevant for paediatric diseases.
6. Eliminate the age threshold (often at 18 years old) differentiating adult from adolescent oncology patients to increase teenagers participation in potentially life-saving clinical trials.

