

# **Commission Report on the Paediatric Regulation (Article 50(3) of Regulation (EC) No 1901/2006) Consultation Document**

## **Response from Bone Cancer Research Trust**

### **Reference: PCPM/16 – Paediatric Report**

This is a response to the paediatric regulations consultation paper from the Bone Cancer Research Trust, a charitable organisation funding research, raising awareness and providing information and support to those affected by primary bone cancer.

Bone cancer is a rare cancer, affecting approximately 500 people annually in the UK. It is known to affect a range of ages; affecting adults as well as frequently occurring in children, teenagers and young adults. Therefore, as a charity dedicated to patients affected by bone cancer, our focus during this consultation lies with paediatric oncology, although we do not wish to diminish the importance of other paediatric conditions.

Bone Cancer Research Trust consent to publication of all information in whole or in part, including our organisation name. We declare that nothing within the response is unlawful or would infringe the rights of any third party in a manner that would prevent publication. Contact regarding this consultation document should be sent to [info@bcrt.org.uk](mailto:info@bcrt.org.uk).

### **1.1 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?**

Agreement that the legislation supporting the development of paediatric medicines was necessary due the widespread use of off-label medicines in the paediatric population. The regulation aimed to increase the accessibility of medicinal products for use in the paediatric population and ensure these products were subject to high-quality research and appropriate authorisation.<sup>1</sup>

Much required progress has been made and important steps have been taken. Since the implementation of the Regulation, from 2007 until 2015, 238 new medicines for use in children and 39 new pharmaceutical forms appropriate for children were authorised in the EU. The regulation has led to successful changes in the development of paediatric medicines, the information available for paediatric medicines and the overall awareness of paediatric needs.<sup>2</sup>

However, there are still improvements to be made and benefits for paediatric oncology have been sparse. There have been 2 paediatric oncology medicines authorised based on data from studies in agreed PIP's.<sup>2</sup> Adjustments and improvements to the regulation are required to improve the development of ethical, high quality and appropriately authorised medicines for the paediatric population.

## 1.2 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?**

In agreement that the consequence of the current approach lies with progress in paediatric medicines relying on the company's adult product pipeline and advances required in adult populations. Adult conditions do not necessarily overlap with paediatric conditions, leaving a considerable amount of paediatric conditions that are not investigated to their full potential and therefore receive no benefit from the paediatric regulation.

Each year, approximately 15,000 children under 15 years of age and 20,000 teenagers and young adults (15 to 24 years of age) are newly diagnosed with cancer in the EU alone. Leading to around 6,000 deaths in the EU each year of children with cancer.<sup>2</sup>

Therefore we support the following from SCIOPE's position statement:

*'Thus, the EU Paediatric Medicines Regulation has benefited many childhood disease – but not yet sufficiently cancer, which remains the most urgent human, social and public health issue in England'.<sup>3</sup>*

Cancers that affect children are biologically different to those affecting adults and in the main are relatively rare and therefore lack financial attractiveness to pharmaceutical and biotechnology companies. Therefore it is not viable to continue to investigate paediatric oncology medicine through the current format of the paediatric regulation that heavily relies on the adult product pipeline. Research has taught us that targeting a specific mechanism of action is more effective than targeting a condition or tumour type directly.

Therefore, do not agree with the statement that the paediatric regulation *'is an important enabler, but as far as their effect is concerned, they are partly dependant on factors that can hardly be influenced by legislation'*. Further development of the functional and rewards system will enable the legislation to have a far-reaching beneficial effect by encouraging paediatric-specific investigations and increasing the therapeutic areas that the regulation contributes to.

### 1.3 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 EMA's 10 Year report makes clear that there has been no significant increase in paediatric medicines for cancer.

Furthermore, waiver requests in the field of paediatric oncology are high in both product specific waivers (where the medicine was deemed not to provide a benefit to the paediatric population), at 9% of waiver requests, and in class waiver revisions when a medical condition does not occur in children and so a waiver is requested by the pharmaceutical company; of which 60% of these requests were concerned with oncology developments.<sup>2</sup>

There are potential medicines that are missed opportunities due to their lack of significance in adult conditions or because a condition does not occur in children. Adjustment of the regulations waivers required to terminate a study should require the drugs mechanism of action to be established and investigated in the Paediatric Investigation Plan (PIP), in the hope to reduce the number of missed opportunities in paediatric-specific conditions.

We support The Institute of Cancer Research that:

*'Pharmaceutical companies are currently given class waivers from testing potentially important cancer drugs in children because the drugs are being registered for adult cancers that do not occur in children – even though the drugs may work in a way that could be effective against paediatric cancers. We support replacing the class waiver system with one that looks at the mechanism of action of the drug and feel this single change would have the greatest impact on increasing access to clinical trials for children and adolescents'.<sup>4</sup>*

There also needs to be increased incentives and knowledge sharing to encourage new drug use by healthcare professionals when these drugs do come through development.

### 1.4 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 costing of 20 million Euros is noted as reasonable, which may not be the case for smaller companies where important progress is made. A clear system of rewards is required for companies developing PIP's to increase incentives.

## 1.5 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?**

Agree that early, strategic, planning will usually ensure a reward. However, the incentives and rewards available are long-drawn out and there are concerns of the likelihood of a failure of a drug in an adult condition resulting in a cancellation of the corresponding PIP, even though potential benefit for children may remain.

We support Unite2Cure in their view that:

*'The balance between the cost of an oncology PIP and the possible reward is not sufficiently attractive to the pharmaceutical industry. Furthermore, the delays before financial return is forthcoming are a disincentive.'*

Incentives to encourage paediatric investigations to conditions that are not associated to a corresponding adult condition are necessary, as is the ability to offer rewards sooner.

## 1.6 The Orphan Reward

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

We support The Institute of Cancer Research that:

*'Orphan drug designation has not proved effective at providing financial incentives for companies to develop drugs solely for paediatric cancers. No cancer drugs have gone through this process purely for childhood cancers, indicating that companies do not regard it as financially attractive. Instead, we believe that an improved PIP process should be the main route for developing paediatric medicines'.<sup>4</sup>*

## 1.7 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 recognise that necessary improvements have been made over time. For example, the revision of class waivers following recognition that the existing class waiver list limited the opportunity to consider potential pharmaceutical benefits for children is a positive step.

Furthermore, we believe the launch of the Enpr-EMA in 2009 to facilitate the conduct of clinical trials is an improvement in order to overcome hurdles in research infrastructure and creates the collaborative network required to push forward high-quality research and expertise. The lack of research infrastructure was identified by the Enpr-EMA and efforts are now made to ensure sustainable paediatric research and raise awareness of the need and support for clinical trials in the paediatric population amongst healthcare professionals, patients and parents.

## 1.8 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?**

Agreement that the 2015 review of class waiver decisions is a positive motion. However, voluntary research can not be relied on to produce benefits in currently neglected areas, such as paediatric oncology. Investigation into the 'mechanism of action' principle is highly required.

The EMA's 10 year Report acknowledges paediatric oncology as a neglected therapeutic area and the requirement for the mechanism of action principle to be investigated:

*'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 anticancer medicine where the anti-cancer adult indication is under development.'*<sup>2</sup>

As detailed in Section 1.3 of this consultation, the waiver mechanism results in a high proportion of oncology medicines being granted a waiver and this can result in missed opportunities for paediatric

cancer patients. In relation to this, there are few paediatric clinical trials in this area have been developed.

*'The number of new phase 1 paediatric oncology trials seems limited in the EU compared to the U.S.*

*In comparison with the new medicines authorised to treat a cancer in adults, the number of paediatric early trials is small'.<sup>2</sup>*

A well-known example of a missed opportunity is the drug Crizotinib, a targeted anticancer drug to ALK+ lung cancer. As lung cancer does not occur in paediatric populations this drug was class waived for development in the paediatric population. However, ALK rearrangements, as targeted by Crizotinib, are present in numerous paediatric malignancies including anaplastic lymphoma, soft-tissue sarcoma and neuroblastoma. Crizotinib development began in the U.S in December 2009 and showed a high-level of activity for children with lymphoma and sarcoma. This is an obvious example of the paediatric population in the EU being denied access to a drug due to the adult cancer being studied not occurring in children. An inhibitor to ALK has since been developed voluntarily, but voluntary investigation cannot be relied on to allow EU pediatric populations access to beneficial drugs.<sup>3</sup> This example alone emphasises the need to alter the waiver system and increased focus on the mechanism of action principle. Further examples of missed opportunities and delays can be found in SCIOPE's position statement.

## 1.9 Deferral

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

Deferrals are a matter of significant concern because of the potential to delay the paediatric populations access to medicines and recruitment to paediatric clinical trials.

As the consultation states, further frustrations relative to deferrals lie with clinicians, parents and patients after adult authorisations take place yet delays for paediatric authorisations continue.

*'Parents often fail to see the added value of agreeing that their child participates in clinical research if the adult product can already be used (off-label) in children. Moreover, long deferrals may undermine the enforceability of paediatric requirements, and the availability of the reward, especially if the deferral ends after protection periods for the product have expired'.*

## 1.10 Voluntary Paediatric Investigation Plans

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

It is positive that voluntary paediatric investigation plans have occurred, but the system cannot rely on these forthcoming and further incentives are required to encourage this and push forward paediatric investigations. Increased knowledge and awareness of the potential of voluntary paediatric investigation plans may be beneficial, particularly for those areas with high unmet need, namely paediatric oncology.

## 1.11 Biosimilars

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

No comment

## 1.12 PUMA – Paediatric-Use Marketing Authorisations

### 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?

In agreement that the Paediatric-Use Marketing Authorisation (PUMA) concept has had disappointing outcomes in its attempt to transform off-label products into authorised and safer product use in paediatrics.

As the EMA's 10 yr report states:

*'For this group of medicinal products, the incentives such as data exclusivity, do not seem attractive enough. Trials are difficult to perform as these medicines are available on the market and often widely used off-label, and health professionals may not be motivated to study older medicines'.<sup>2</sup>*

### 1.13 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?**

Overall, the percentage of clinical trials involving children has increased from 9.3% to 11.5% from 2015-2016. We do not feel this is a substantial increase in participation.

We believe the assumption of vulnerability in the paediatric population may in some aspects be damaging to the progression of research in this area. Improved, age-appropriate, communication of clinical research to both patient and parent is required in order to relieve this feeling of vulnerability by improving knowledge and thus willingness to partake in trials.

Therefore, we strongly agree with the statement from the Nuffield Bio-ethics regarding research with children:

*‘Central to the report is the idea that from a young age, 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. The risk of children being placed in vulnerable situations can be minimised by ensuring that researchers engage with children’s and parents’ views and experiences in the prioritisation, design and review of research and that research is subject to appropriate scrutiny and governance. Children and parents should be confident that an invitation to take part in research is a ‘fair offer’ where the value of the research and its risks and benefits, have been independently assessed’.<sup>5</sup>*

In contrast, not including children or presuming vulnerability is denying children and their families the opportunity to participate and contribute to meaningful research.

The Enpr-EMA mission is clear and positive, establishing a network of specialists, investigators and centers with expertise in carrying out paediatric clinical trials while raising awareness of the need for such trials. Encouraging this collaborative network and engagement with patient organisations is promising and required in order to improve recruitment rates to such trials.

A recent review (Friend et al, 2016) states that adolescent and young adult patients fare better when enrolled in a clinical trial, yet are much less likely to participate in trials in comparison to adults and children.<sup>6</sup> This is due to regulatory barriers placed on trials in terms of age-brackets of under 16’s classed as children, yet those aged 18 and over are classed as adult. These arbitrary age restraints are limiting and many studies show that trial protocols should be relative to the patient’s tumour biology rather than their age. In the UK, two trials for bone sarcoma (EUROMOS-1 and EURO-



EWING-99) opened the age eligibility to 0-40 years and 0-50 years, respectively, to improve trial recruitment.

### **1.14 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?**

We support the view shared by SCIOPE and Unite2Cure that fees should be paid to the paediatric committee for their expertise and scientific advice. Such fees would encourage expansion and sustainability of the paediatric committee and external advisors in sharing their knowledge and time.

### **1.15 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 had a clear positive impact on paediatric research in establishing collaborative networks, increasing awareness of paediatric research and encouraging paediatric investigations.

However, the overarching effect of the Paediatric Regulation is judged on its impact in increasing drug development for the paediatric population and the benefits this has for patients.

### **1.16 “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?**

Genome profiling and personalised medicine techniques are large trends in numerous areas, particularly oncology. These methods of defining specific gene targets for therapeutics is compatible with the ‘mechanism of action’ principle and increasing opportunities for paediatric investigation plans.

Friend et al (2016) states that next generation sequencing is starting to become a very useful tool, allowing providers to understand variations in cancer biology which may affect individual treatment plans, including whether a patient should be treated according to a child or adult protocol.<sup>6</sup>

Ultimately, the addition of the 'mechanism of action' principle to PIP's will allow these promising and emerging trend to become beneficial to the paediatric population.

### **1.17 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 strongly 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 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.
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

In addition, we believe it is worth commenting on that whilst this consultation is in regard to the paediatric regulation, bone cancers occur across the age continuum and are rare cancers. Many of the point raised in this consultation to improve the paediatric regulation, such as the mechanism of action principle and the need to focus on biological targets rather than just the tumour type, are relevant because of the rarity of paediatric cancers and are therefore equally as relevant to rare cancers as a whole which affect a variety of age groups.

## References:

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