SIOP EUROPE RESPONSE TO THE EUROPEAN COMMISSION PUBLIC CONSULTATION ON EXPERIENCE ACQUIRED AS A RESULT OF THE PAEDIATRIC REGULATION

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SIOP Europe, the European Society for Paediatric Oncology (SIOPE) would like to thank the European Commission for the opportunity to contribute to the Public Consultation on the EU Paediatric Regulation EU Clinical Trials Directive Consultation process, allowing the experience of the pan-European, multidisciplinary Board of SIOPE, to be considered.

SIOPE is a specialised network of health professionals working in the field of childhood cancers in Europe. It is the only multidisciplinary, pan-European organisation dedicated to paediatric oncology and it exists to address the main challenges in childhood cancer such as promoting and supporting collaborative clinical trials within Europe, furthering education and training for health professionals, increasing awareness on and around childhood cancers and improving information exchange and dissemination across borders.

Established in 1998 with an office based in Brussels since 2007, SIOPE is the continental branch of SIOP (the International Society of Paediatric Oncology), a Founding Member of the European CanCer Organisation (ECCO), and a member of Eurordis – Rare Diseases Europe, the European Forum for Good Clinical Practice (EFGCP) and Rare Cancers Europe. Representing multinational clinical trials groups and national childhood organisations, SIOPE develops novel strategies for cancer awareness, cancer diagnosis, and cancer treatment focused on children.

Aware that a highly dedicated multidisciplinary approach to treatment as well as investing in high-quality clinical research can greatly increase survival rates, SIOPE actively encourages greater coordination of clinical trials activity in Europe, as well as supporting education and exchanges between all professionals working in the field of paediatric oncology. SIOPE additionally maintains strong links with national patient organisations ensuring a strong patient perspective is maintained, as well as keenly promoting information dissemination of the latest development in cancer research and EU policy.

Paediatric Oncology and Drug Development

In paediatric oncology, within the last 30 years, available anticancer drugs have been prospectively studied in clinical trials run by the academic networks without the help of the pharmaceutical industry and significant progress has been achieved in the outcome of many paediatric malignancies. **To date, children in Europe have been denied access to innovative anticancer therapies while in the meantime many truly innovative medicines have been developed for the treatment of adult cancers**.

As more than 3,000 children die of cancer in Europe each year, there is an urgent requirement to speed up the development of safe and effective anticancer therapies for children and adolescents. Cancer is a rare disease in the paediatric population, as opposed to adults, and significant progress has been made during the last 50 years to improve the cure rate. However, cancer remains the first cause of death by disease beyond the age of one year in Europe, and this is a health issue that needs to be addressed at European level.

Nowadays, targeted therapies have demonstrated their ability to be effective against refractory diseases in adults, such as melanoma, lung cancer, chronic myeloid leukaemia and gastrointestinal stromal tumours. More than 800 new anticancer compounds are in development in adults, with the medicines targeting specific molecular alterations that play a major role in the growth and metastasis of malignant tumours. Only a subset of patients suffering from a cancer (for example, a lung cancer) has a relevant molecular alteration in their tumour, with tumour biomarkers used to identify which patients should be treated by a given targeted therapy.

The same molecular alterations are observed in paediatric malignancies even though they are of different types. For example, anaplastic lymphoma kinase (ALK) is a gene altered in 4% of lung cancers in adults, and 10% of patients with neuroblastoma, a disease occurring in children only. While it is not the case currently, it makes sense that any ALK inhibitor should be developed both in adults and children. **Targeted therapies open new opportunities for safe and effective anticancer for children and adolescents with cancer**.

The European paediatric oncology community is ready to run new drug development in a professional way and to address children's needs. Indeed, European research networks have been set up to speed up new drug development under the umbrella of SIOPE and the Innovative Therapies for Children with Cancer (ITCC) European network runs early drug trials (Phase I and II trials) based on the identification and validation of relevant molecular alterations in paediatric malignancies. Joint projects are run between the ITCC and each of the different European tumour groups to address new drug development down to late Phase II and III trials.

International collaboration is increasing, between Europe (the ITCC network), the US (the Children's Oncology Group Phase 1 consortium, and the Pediatric Oncology Experimental Therapeutics Investigators Consortium and Therapeutic Advances in Childhood Leukemia and Lymphoma consortium networks), Canada (the C17 consortium) and Australia (the Australian Children's Cancer Trial Group) to better address together the issue of paediatric anticancer drug development, especially in extremely rare situations.

The **European Network for Cancer Research in Children and Adolescents (ENCCA)**, a network of excellence, launched in 2011, is a four-year project funded by the EU-funded 7th Framework Programme to structure paediatric oncology research in Europe and to provide strategy, tools and platforms to achieve the goals of the next 15 years: to increase both cure rate and quality of cure for children and adolescents with cancer. With 34 partner institutions and organisations from 11 different European countries, we hope this important network can have a positive and long-term impact and provide a brighter future for young cancer patients in Europe.

We wish the European Commission success in analysis of the consultation responses and welcome the opportunity to discuss the issues raised in this response in greater detail.

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1. A CHANGE OF CULTURE: NOWADAYS PAEDIATRIC DEVELOPMENT IS AN INTEGRAL PART OF PRODUCT DEVELOPMENT

Consultation item No 1: Do you agree that the Paediatric Regulation has paved the way for paediatric development, making it an integral part of the overall product development of medicines in the European Union?

The Paediatric Regulation changed the field of new oncology drug development for children and adolescents with cancer and paved the way for optimal paediatric development. There are many more opportunities for interactions with the pharmaceutical industry, than in the past.

However, so far, the needs of children with cancer have not been adequately addressed. Drugs of major interest for paediatric malignancies have been waived because the adult condition does not exist in the paediatric population, while its mechanism of action is perfectly relevant for a paediatric use. Several Paediatric Investigational Plans (PIPs) have been approved in very rare conditions or situations and proved to be extremely difficult to run and not feasible while diseases that kill children have been ignored because of the class waiver concept. In addition, most pharmaceutical companies consider paediatric drug development as a regulatory obligation to comply with and not a full R&D programme to be discussed and designed with cooperative clinical trial groups. SIOPE considers that this is not the best way to warrant that PIPs will adequately address paediatric oncology needs.

2. HAS THE REGULATION DELIVERED IN TERMS OF OUTPUT? TOO EARLY TO JUDGE.

Consultation item No 2: Do you agree with the above assessment?

No, we the SIOP Europe Board do not agree.

Five years of implementation of the Regulation and only one oncology drug approved through a PIP is extremely disappointing!

PIPs are too long, too comprehensive, too detailed and the vast majority of them are deferred. This explains why they did not deliver better results over these first five years of implementing the legislation. Unfortunately, there was no increase in the number of new drugs in early development. This is a major drawback and compares poorly with the number of drugs accessible in the US.

3. THE PUMA CONCEPT: A DISAPPOINTMENT

Consultation item No 3: Do you share this view? Could you give specific reasons for the disappointing uptake of the PUMA concept? Is it likely that PUMA will become more attractive in the coming years?

The need for studies on off-patent oncology drugs is not extensive in the field of paediatric oncology as Europe has a large and comprehensive academic clinical research programme running (including phase I, II and III) using off-patent medicines for the last 50 years. This explains why the cure rate for children and young people with cancer has successfully increased from less than 30% in the 1960s to 80% nowadays. Information on most off-patent drugs has thus already been generated through this prospective high-quality clinical research and they are used in standard care.

The major challenge in this field is the need for new, innovative drugs that should have been provided largely through PIPs. This is where priority should be given.

Few oncology projects have been funded through the EU-funded Seventh Framework Programme (FP7) off-patent medicine calls with a PUMA objective. They were focused on the development of age–appropriate oral formulation of largely daily used cytotoxic agents (an important need which was unlikely to be developed by the generic companies) and pharmacology of anticancer chemotherapy in infants.

An important point to add is that FP7 funding, while helpful, involves complicated procedures and is not easy to use to run clinical trials.

This explains why few PUMAs have been submitted for oncology drugs.

4. WAITING QUEUES? NO EVIDENCE OF DELAYS IN ADULT APPLICATIONS

Consultation item No 4: Do you agree that, generally speaking, the paediatric obligations have no impact on timelines in adult development, as there is no evidence for delays in marketing authorisation applications for reasons of compliance with the paediatric obligation? If you feel that there is an impact, practical examples would be appreciated.

Through consultation with our colleagues in the adult oncology domain, there is not a single example of an oncology drug with a delayed marketed authorisation (and thus delayed access for adult patients) due to the obligations of the Paediatric Regulation.

5. MISSING THE POINT? PAEDIATRIC DEVELOPMENT IS DEPENDENT ON ADULT DEVELOPMENT, NOT PAEDIATRIC NEEDS

Consultation item No 5: Do you have any comments on the above?

We fully acknowledge that drug development is company-driven in a competitive way and normally focussed on areas where there is a market. However, the Paediatric Regulation ignored the fact that the same oncology drugs are used to treat both adult and paediatric malignancies, even though they are different with different histology. This is a major drawback.

6. THE BURDEN/REWARD RATIO —A BALANCED APPROACH?

Consultation item No 6: Do you agree with the above?

While efforts have been made to improve the regulatory process and make it easier, it remains too complicated and slow. From our understanding, **regulatory obligation** has been the main driver of the PIP activity while the positive impact of effective reward cannot be assessed at the moment.

7. ARTICLES 45/46: THE HIDDEN GEM OF THE PAEDIATRIC REGULATION

Consultation item No 7: Do you agree that Articles 45/46 have proved to be an efficient and successful tool for gathering and compiling existing paediatric data and making it available to the competent authorities and subsequently, via databases, to the interested public?

From the academic viewpoint, at this stage it is not possible to adequately evaluate the true output of this huge activity (article 45/46) being performed both by the European Medicines Agency (EMA) and pharmaceutical companies.

8. LOST IN INFORMATION: HEALTHCARE PROFESSIONALS NOT AS RECEPTIVE AS EXPECTED

Consultation item No 8: Do you agree that healthcare professionals may not always be as receptive to new scientific information on the use of particular products in children as might be expected? Do you agree that this problem has to be addressed primarily at national level? How could healthcare professionals be more interested and engage in paediatric clinical research?

In paediatric oncology, healthcare professionals are very receptive to new scientific information and are eager to propose safe and effective innovative treatments to those young patients who have poorer outcomes with many side effects and who still die of cancer.

Paediatric oncologists are still in a situation of prescribing off-label new drugs (which are commercially available) to children with life-threatening diseases and no curative therapeutic options, as standard practice.

The Paediatric Regulation was highly anticipated and was expected to increase significantly the number of new drugs in early clinical trials to propose access to innovation for patients in a safe and controlled way.

However, unfortunately the regulation failed since there is no increase in early clinical trials.

Thus, off-label used is still important and the introduction of effective targeted agents on the market is likely to continue to increase off-label use of promising drugs (with information available on the internet for parents and family members) in paediatric malignancies.

9. CLINICAL TRIALS WITH CHILDREN: NO SPECIFIC PROBLEMS DETECTED

Consultation item No 9: Do you have any comments on developments in clinical trials with children following the adoption of the Regulation and in view of the above description?

Under the EU Clinical Trials Directive (**2001/20/EC)** which is currently being revised, the obstacles for initiating clinical studies in children have been a major challenge and should be underlined. The development of clinical trials is much too slow and requires means that are not easily achievable, at least in the academic setting. There has been an immensely negative impact on investigator-driven clinical trials. Thus, the need for an EU 'Clinical Trials Regulation' that facilitates academic trials, is a major one.

10. UNNECESSARY EFFORTS? NON-COMPLETED PAEDIATRIC INVESTIGATION PLANS

Consultation item No 10: Do you have any comments on this point?

It is essential to make a comprehensive evaluation of the efficiency of the PIP process. The resources mobilised by all parties (the EMA, the EMA Paediatric Committee (PDCO), and the academic community) for a long PIP evaluation process ending with an extensive detailed programme to be run over more than 6 to 10 years, should be compared to the number of PIPs on-going and completed. At the moment, we feel that there is a major imbalance.

From our point of view, there is a need to simplify the entire process, to simplify the content of PIPs, to increase the likelihood that PIPs will be feasible and will meet the needs of young patients, in order to improve the performance of the entire process.

In our estimation, at this point in time, the output in terms of clinical research and probability of success is not in line with the immense activity by PDCO, EMA and the pharmaceutical industry.

11. SOPHISTICATED FRAMEWORK OF EXPERTISE ACHIEVED

Consultation item No 11: Do you agree that the Paediatric Regulation has contributed substantially to the establishment of a comprehensive framework of paediatric expertise in the European Union?

The European paediatric oncology community is a close-knitted network of experts from across Europe that have efficiently collaborated and delivered, and continue to deliver the best possible treatment and care for young people with cancer. In terms of clinical research, to improving cure rate and quality-of-cure is the absolute priority. As a result of this long-established way of working, the Paediatric Regulation has had little effect on the structuration of the European paediatric oncology research network.

However, the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) initiative (that includes four cancer networks) has been a positive development, allowing paediatric groups to share knowledge, challenges and best practice in order to identify common solutions across several paediatric diseases.

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