EU PHARMACEUTICAL STRATEGY:
LET'S NOT FORGET CHILDREN AND ADOLESCENTS WITH CANCER

Attachment to
SIOP Europe – CCI Europe – PanCare response to the EU Pharmaceutical Strategy Roadmap Consultation

About SIOP Europe (www.siope.eu)
The **European Society for Paediatric Oncology (SIOP Europe, or SIOPE)** is the single, united European organisation of academia and healthcare professionals dedicated to childhood and teenage cancer and is working in close partnership with patient, parent and childhood cancer survivor groups across Europe.

About CCI-Europe (www.ccieurope.eu)
Chilhood Cancer International - Europe (CCI-Europe) represents childhood cancer parent and survivor groups as well as other childhood cancer organisations in Europe. CCI Europe works together with all relevant stakeholders for the same aim: to help children and adolescents with cancer to be cured, with no - or as few as possible - long term health problems/late effects.

About PanCare (**www.pancare.eu**)
The **Pan-European Network for Care of Survivors After Childhood and Adolescent Cancer (PanCare)** is a multidisciplinary pan-European network of professionals, survivors and their families that aims to reduce the frequency, severity and impact of late side-effects of the treatment of children and adolescents with cancer.

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EUROPEAN CHILDHOOD CANCER COMMUNITY RESPONSE
TO THE EU PHARMACEUTICAL STRATEGY ROADMAP CONSULTATION

The European childhood cancer community: SIOP-E, CCI-E, and PanCare welcome the EU Pharmaceutical Strategy with the strong hope that it can deliver urgently needed improvements for the over 6,000 children and young people dying of cancer each year in Europe.

Although individually rare, all paediatric cancers together are a leading cause of disease- related mortality in children and adolescents and lead to long-term morbidity in most survivors.

Little progress has been made for high-risk paediatric tumours due to lack of access to targeted innovation. Access to essential medicines has also been uneven. The new EU Pharmaceutical Strategy can make a life-saving difference for young cancer patients.

INNOVATION

Despite their high collective burden, the rarity of individual paediatric cancers has translated into very limited market-driven innovation. Only 9 anti-cancer medicines were authorized for a specific paediatric indication since 2007, in contrast to over 150 for adult cancers. The slow pace of innovation cannot serve paediatric cancer patients appropriately across the variety of specific malignancy sub-types that affect this population. Progress requires solid support for dedicated international academic research platforms, cross-linked to and informed by adult cancer and industry-driven research, and regulatory changes.

The EU Orphan Regulation has been ineffective for paediatric cancer medicine development. The Paediatric Regulation was expected to potentially be more relevant but left paediatric cancer needs largely unmet. Childhood cancer stakeholders have been working as part of ACCELERATE (www.accelerate-platform.org) to formulate evidence-based recommendations for improvement and to implement solutions. These include:

- Mechanism-of-action rather than adult clinical indication-driven investigation,
- Alignment with the global regulatory developments such as the RACE for Children Act,
- Tapping into the potential of repurposing molecules originally meant for development in adults,
- Incentivising development of medicines targeting cancers in children specifically, based on their distinct biological alterations with relevance for therapeutic intervention,
- Early access to new medicines for children and adolescents with cancer in the development phase.

Harmonization of clinical trials approval across the EU is also key.

The European Commission recognised the need to evaluate the regulatory framework and implementation more closely. We welcome this effort so that the needs of children and adolescents with cancer are fully and urgently considered.

ESSENTIAL MEDICINES

According to a survey of the EU Joint Action on Rare Cancers (2016-19), young cancer patients in Europe still experience lack of access to essential medicines due to:

- Shortages,
- Lack of child-friendly formulations,
- Financial inaccessibility in some countries and for newer medicines,
- Inconsistent provision of pain control during procedures and course of disease.

EU action on essential medicines should consider issues that affect young cancer patients and refer to the WHO Essential Medicines List for Children and the evidence generated by the European paediatric cancer community with EU programme support.

(CONT.)

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PRICING

Newly authorized targeted agents and immunotherapy medicines for paediatric cancers are gradually entering the market. Appropriate pricing and reimbursement strategies are a must considering the potential life span gained through successful treatment in this age group. Harmonization or centralisation of HTA assessments would facilitate equality of access.

OUTCOME DATA COLLECTION

To adequately monitor the optimal use of medicines, it is critical to invest in outcome research, including on possible late effects in survivors.

CONCLUSION

The EU Pharmaceutical Strategy is a unique opportunity to address the major unmet needs in paediatric cancer. We urge the Commission to seize this chance to make a pivotal change for our youngest citizens and society at large.

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PAEDIATRIC CANCER MEDICINES: URGENT NEED TO SPEED UP LIFE-SAVING INNOVATION

Position statement by SIOP Europe – Unite2Cure & CCI-Europe – CR UK (last updated: July 2020)

Each year 6,000 children and young people die of cancer in Europe - it remains the first cause of death by disease beyond one year of age. Lack of access to innovative medicines is a key problem.

In 2007 the EU Paediatric (Medicines) Regulation (EC No 1901/2006) was launched with the aim to meet the specific therapeutic needs of children with better evaluated and authorised medicines. The core principle of the Regulation is that every time pharmaceutical companies introduce a product for authorisation to market it in Europe for the treatment of an adult disease, they should evaluate it for use in children through a Paediatric Investigation Plan if there is an unmet therapeutic need.

In childhood cancer, significantly increased access to innovative therapies can save lives, and the community had therefore welcomed this EU initiative.

Unfortunately, more than ten years since the entry into force of the EU Paediatric Regulation, less than 10% of children with terminal cancer have access to new, experimental drugs which could give them a second chance in life, and only nine (9) innovative targeted anti-cancer drugs were authorised for a paediatric malignancy.

Thus, the EU Paediatric Regulation has benefited many childhood diseases - but not yet sufficiently cancer, which remains a most urgent human, social and public health issue in Europe.

The Regulation has nevertheless led to an increased multi-stakeholder dialogue and cooperation on childhood cancer drug development and the ACCELERATE platform where, by working together, academia, parents, industry, and charities had identified existing bottlenecks and formulated specific proposals for the improvement of the Regulation.

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.

Background: The Regulation currently allows a waiver to the requirement to undertake a Paediatric Investigation Plan where a drug is intended to treat an adults-only disease, such as lung cancer. However, there is ample evidence that the way a drug works in an adult cancer can be relevant to a cancer type that occurs in children. (Examples 1 and 2)

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.

Background: More than 1000 oncology drugs are in development in adults and often companies develop drugs with the same mechanism of action. Currently, a multitude of Paediatric Investigation Plans undertaken without mutual consultation between companies and targeting the same condition in children proved to be unfeasible to complete.

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.

Background: Major delays have been documented in starting clinical trials of oncology drugs for children while waiting for the drug to show promise in adult cancer patients – these are missed opportunities for young people with life-threatening malignancies to have a potentially effective treatment. (Example 3)

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.

Background: Only two innovative, specific paediatric drugs have been approved so far, suggesting that the incentives are insufficient to encourage and increase investment in the field of specific paediatric drugs. In addition, the development of several drugs has been stopped in adults for inefficacy, but they have not been considered for a development in the paediatric population (repositioning) even though there was a scientific and medical rationale.

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SELECTED EXAMPLES

Example 1: Unjustified waiver: crizotinib

Crizotinib is a targeted anticancer drug for the treatment of ALK+ lung cancer. Lung cancer does not exist in children and the drug has been class waived for its development in the paediatric population.
ALK rearrangements are observed in several paediatric malignancies: anaplastic lymphoma, soft tissue sarcoma, neuroblastoma, making crizotinib a relevant and important drug to evaluate in children based on its mechanism of action.

- The paediatric development of crizotinib started in the US in December 2009 and showed high level of activity in children and adolescents with lymphoma and sarcoma as well as some activity in children with neuroblastoma.
- In Europe, children and adolescents with ALK+ relapsed malignancies have been denied access to an ALK inhibitor until ceritinib, another ALK inhibitor, has been voluntarily developed in children (February 2013).
- Currently, there are major inequalities in Europe for children accessing crizotinib as: i)very few academia-driven trials are ongoing; ii) the drug is prescribed off label in some countries; iii) most children with an ALK+ malignancy do not have access to an ALK inhibitor.

Example 2: Unfeasible PIPs – Vemurafenib

Vemurafenib is a targeted anticancer drug for the treatment of B-RAF mutated melanoma, approved in the US in 2011 and in Europe in 2012.

- B-RAF metastatic melanoma is extremely rare in adolescents and B-RAF mutations are found in several paediatric malignancies, such as brain tumours (high grade and low grade gliomas) and histiocytosis.
- Thus, the adult indication (melanoma) is extremely rare in adolescents but the mechanism of action is relevant for several paediatric malignancies.
- A PIP was granted in April 2011 to study vemurafenib in B-RAF advanced metastatic melanoma in patients aged 12 to 18, only.
- The paediatric clinical trial started in January 2011 and is open in 26 investigating sites in 10 countries and 4 continents. As of December 2015 and with the drug now being commercially available and because of the limited focus of the paediatric development plan, only 6 adolescents have been recruited on trial.

Example 3: Major Delays – Pembrolizumab and Nivolumab

- Pembrolizumab and Nivolumab are the first PD1 inhibitors approved for the treatment of melanoma in September and December 2014 in the US, respectively, and in July 2015 in Europe.
- These immunotherapy medicines have also a significant activity in several other adult cancers, such as lung cancer, kidney cancer, bladder cancer, Hodgkin disease and a very large portfolio of trials explores currently several PD1 and PDL1 inhibitors in all adult malignancies.
- The paediatric development of Nivolumab and Pembrolizumab started in early 2015 i.e. after they were granted a market approval in the US.
- The effective development of PD1 inhibitors in children has been delayed and we are unaware if this class of drugs will benefit children.

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ESSENTIAL MEDICINES FOR PAEDIATRIC CANCER: CONCLUSIONS FROM JOINT ACTION ON RARE CANCERS (2019)

RESULTS OF SURVEY ON AVAILABILITY & ACCESSIBILITY OF MEDICINES FOR PAEDIATRIC CANCERS

Although essential medicines used to treat children and adolescents with cancer are old and mostly off-patent, parents and health professionals across Europe still experience issues of access to these agents.

- **Shortages of medicines** were reported as the most common reason for lack of availability, with potentially critical implications for children's lives.

- **Budget limitations at the country or hospital level** are still pronounced in some EU countries, particularly those with a relatively low health expenditure rate.

- **Lack of child-friendly formulations** is an important issue potentially preventing children from taking the anticancer medication as prescribed.

- There are major **differences in pain control accessibility** for children and adolescents undergoing cancer treatment across Europe.

RECOMMENDATIONS TO ACTORS AT THE EUROPEAN LEVEL

- Establish a **European level reference lists of essential medicines in concertation with health professionals and parent representatives** (see next item – SIOP Europe Essential Medicines project) and set up a coordinated initiative with EU Member States and other European countries to monitor and anticipate shortages;

- Support policies, programmes and projects to o**vercome inequalities in access to essential medicines and supportive and palliative care used in children adolescents with cancer** across Europe;

- **Support further research on access to medicine**s used for the treatment and supportive and palliative care of paediatric malignancies across Europe;

- Support initiatives to foster **availability of child-friendly doses and formulations** of essential anticancer medicines for the paediatric population;

- **Adequate supportive and palliative care services are necessary** for children, and opioids that manage cancer pain are inexpensive and should be provided to avoid that children suffer unnecessarily.

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SIOP EUROPE ESSENTIAL MEDICINES PROJECT (2019 – ongoing)

BACKGROUND

The survey conducted by SIOP Europe and CCI-Europe in the Joint Action on Rare Cancers (JARC, 2016-2019) identified four issues in the access to essential medicines for paediatric malignancies in Europe:

1. Shortages of medicines are identified as the main access issue,
2. Financial accessibility; cost issues concerned mainly the widening countries,
3. Safe and age-appropriate oral formulations are lacking and
4. Supportive care medicines (including pain medication) are not everywhere/always available.

Furthermore, with the introduction of new and expensive medicines, pricing considerations are gradually becoming pertinent in paediatric cancers.

Following marketing authorization by the European Medicines Agency, it can take years until a new medicine is approved for children with cancer by the national Health Technology Assessment (HTA) agencies. This delay impairs access to new medicines for children.

Lastly, the adult oncology community introduced a clinical benefit scale but not such scale exists for the paediatric population yet.

AIMS AND OBJECTIVES

The aim is to ensure access to all essential treatments for all children and adolescents with cancer, at all times, in the whole of Europe.

The objectives and phases of the project are:

- PHASE 1: Based on current standard treatment protocols in all paediatric tumour types, literature review, and expert consensus, generate evidence for a **European consolidated list of anticancer medicines that are essential for the treatment of children and adolescents with cancer** and should be available at all times (no shortages) for all patients across Europe, and thus contribute to the next revision of the **WHO Essential Medicines List for Children (EMLc) 2021**.

- PHASE 2: Explore the Heath Technology Assessment (HTA) evaluation of recently approved anticancer medicines in a paediatric cancer indication and propose potential solutions to **support HTAs towards a more harmonized cost-effectiveness assessment adopted for the paediatric population**, with the aim to improve affordability of innovative treatments for children and adolescents with cancer across Europe.

METHODOLOGY

SIOP Europe has mobilised the pan-European community of clinicians, researchers, and parents to take part in the project. Activities cover all paediatric tumour types and are led by a leading clinician and clinical trials expert from the SIOP Europe Board, clinicians from Young SIOP Europe committee, senior mentors from European Clinical Trial Groups, and parent representatives from CCI-Europe. Synergies are ensured with the European Reference Network for Paediatric Cancers (ERN PaedCan) and the WHO Global Initiative for Childhood Cancer.
The initiative is currently in Phase 1, where the methodology is to perform a systematic review of medicines currently used in European paediatric haemato-oncology treatment protocols and based on evidence from literature.

The SIOP Europe List of Essential Medicines is expected to be completed by the end of 2020.

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