



Paediatric Cancer Medicines - Urgent need to speed up life-saving innovation

Position statement

September 2016

The time to act to save more children's lives is now
Supporting urgent revision of the EU Paediatric Medicines Regulation

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, nine years since the entry into force of the EU Paediatric Medicine 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 two (2) innovative targeted anti-cancer drugs were authorised for a paediatric malignancy.

Thus, the EU Paediatric Medicines 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 platform¹ where, by working together, academia, parents, industry, and charities had identified existing bottlenecks and formulated specific proposals for the improvement of the Regulation.

On the occasion of the European Commission evaluation of the Paediatric Medicines Regulation and report due in 2017, the pan-European childhood cancer and broader community are calling on the European Institutions to support the urgent revision of the Paediatric Medicines Regulation in line with these mutually agreed multi-stakeholder recommendations:

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. (see 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. (see 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.

¹ <http://www.accelerate-platform.eu/>

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.

Consequences:

- 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.

ANNEX: ABOUT THE STAKEHOLDERS

Unite2Cure

Unite2Cure (www.unite2cure.org) is a network of parents, parent organisations and patient advocates from across Europe, which is calling for better treatment and better access to treatment for children and young people with cancer. This network is supported by many doctors, paediatric oncologists and researchers from all over Europe.

SIOPE

SIOPE, the [European Society for Paediatric Oncology \(www.siope.eu\)](http://www.siope.eu), is the only pan-European organisation representing all professionals working in the field of childhood cancers in close cooperation with parents, patients and survivors. With more than 1,500 members across 31 European countries, today SIOPE is leading the way to ensure the best possible care and outcomes for all children and adolescents with cancer across Europe.

The [SIOPE Strategic Plan](#) - endorsed by all partners in the field - aims to a future where no child dies of cancer and survivors live to the fullest. As a 'European Childhood Cancer Plan', it is based on 7 key objectives and will inspire all future initiatives in this field.

CR UK

Cancer Research UK (www.cancerresearchuk.org) is the world's largest independent funder of cancer research. Cancer Research UK advocates on policy issues across the patient pathway, in particular – at EU level – the regulation of research and prevention.