

## Ten year Report on the European Paediatric Medicine Regulation: Impact on New Drugs for Childrens' Cancers

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## **The 10 year Report on the European Paediatric Medicine Regulation; will it change the landscape of paediatric oncology drug development?**

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In the paediatric oncology community, there was great hope and expectation that the “State of Paediatric Medicines in the EU - 10 years of the EU Paediatric Regulation”<sup>1</sup> report might suggest major alterations in the landscape of development of new medicinal products for children’s cancer. The Report was published by the European Commission on 26 October 2017. Have these expectations been met?

In the last ten years, the European Paediatric Medicine Regulation (EC 1901/2006)<sup>2</sup> has advanced paediatric oncology drug development, but only a very limited number of new medicines have been authorised for cancer in children.

As part of the Regulation, pharmaceutical companies developing drugs of potential interest for childhood illnesses have to create and comply with paediatric investigational plans (PIP) to obtain marketing authorisation for an indication in adults, unless they were granted a product-specific waiver or had a class waiver confirmed by the Paediatric Committee of the EMA. One of the reasons for a waiver is if the indication does not occur in children. To incentivise paediatric studies, companies are rewarded with a 6-month extension of their supplementary protection certificate (SPC) for the investigational drug for successfully completed PIPs.

Over recent years there has been increasing debate that the Regulation should follow a mechanism of action (MOA)-based approach rather than being driven by the adult indication for the medicine. The benefits of a MOA approach, driven by science, have been strongly advocated by the multi-stakeholder forum ACCELERATE, with representatives from academia, pharmaceutical industry, patients and regulatory agencies<sup>4</sup>, amongst others.

We assessed the probable impact of this model by reviewing the MOA of 89 drugs granted a class waiver between June 2012 and June 2015, and considered whether they are active against potential paediatric therapeutic targets. Forty eight (54%) of these 89 drugs had a MOA warranting paediatric development. Two (2%) drugs were considered not relevant and 16 (18%) required further data<sup>5</sup>.

Supported by these analyses, we proposed a MOA-based approach with five initiatives: (i) an aggregated database of paediatric biological tumour drug targets; (ii) a joint academic–pharmaceutical industry pre-clinical platform to analyse the activity of new drugs (Innovative Therapy for Children with Cancer Paediatric Preclinical Proof-of-Concept Platform: ITCC-P4); (iii)

Paediatric Strategy Forums; (iv) molecular profiling of paediatric tumours at diagnosis and relapse; and (v) the suppression of article 11b of the European Paediatric Regulation, which allows product-specific waivers on the grounds that the associated condition does not occur in children<sup>5</sup>. The first three of these have been implemented: a database of targets has been created<sup>6</sup>, –and the ITCC-P4 has been funded as an IMI2 project and is operational<sup>7</sup>. Furthermore, there have been two Paediatric Strategy Forums in 2017 on anaplastic lymphoma kinase inhibition<sup>8</sup> and medicinal product development for mature B cell malignancies. These Forums provided unprecedented opportunities for meaningful interaction between all stakeholders, at a pre-competitive level, on topics that might cause a feasibility problem from an industry or academic standpoint, in paediatric or adolescent cancer drug development.

Globally there is a “wind of change” with the passing of the “FDA Reauthorization of 2017 - Research to Accelerate Cures and Equity (RACE) for Children Act” by the US Congress on 3 August 2017<sup>9</sup>. This Act states that *“development of drugs and biological products should be developed for paediatric cancers, if the drug or biological product is: - (i) intended for the treatment of an adult cancer; and (ii) directed at a molecular target that the Secretary determines to be substantially relevant to the growth or progression of a paediatric cancer.”* Therefore in the US there will soon be an operational MOA-based model for the paediatric development of oncology drugs.

Against this background, what were the conclusions of the “State of Paediatric Medicines in the EU”? The Report demonstrated that the benefits of the Regulation are dependent on companies’ adult product pipeline and influenced by revenue prospects in a specific market. Where the adult market expectations overlap with paediatric therapeutic needs, children sometimes will profit directly e.g. by access to newer drugs developed for diseases such as acute myeloid leukaemia, and certain sarcomas, which may cross the age divide. In contrast, for diseases that are unique to the paediatric population, paediatric development depends on the strategic decision of a company to invest in this area independently of any on-going adult programme. This is particularly true for rare diseases in children; indeed the Report stated *“paediatric oncology is often used as a case study for insufficient advances in an area of high unmet paediatric need.”*<sup>10</sup>

Furthermore, the Report acknowledges that there have been many PIPs for medicinal products for children’s cancer but few of these have been completed. It also stated that there is wide-spread use of the Regulation’s ‘deferral’ system, which leads to delays in paediatric drug development, often until their market of an adult cancer indication is secured.

The Report highlighted the relevance of a MOA approach, but it did not suggest any concrete proposals on how this could be implemented in the EU. It raised a concern that a MOA model could impact upon the predictability of the scope of a PIP and may lead companies to reconsider the overall product development. For paediatric oncology, it stated *“the Orphan Regulation is the relevant instrument given that all paediatric cancers are rare diseases and fall under the EU policy framework on rare diseases. It is not fully understood why companies refrain from reaping the benefit of the Orphan Regulation for paediatric cancers in a similar way that they do for adults”*. The European Commission intends to obtain a better understanding of the combined impact of the Orphan and Paediatric Regulations in diseases which occur only in children. The Commission’s further evaluation of these two regulations aims to provide results by 2019 to allow the next Commission to take an informed decision about possible policy options. It will also allow the forthcoming results of the evaluation of SPC to be taken into account. Unfortunately this two year process is likely to further delay optimization of the regulatory environment to stimulate improvements in drug development for childhood cancer.

We have reviewed 657 oncology orphan drug designations and found 272 (41%) are related to malignant conditions occurring both in adults and children<sup>10</sup>. However, 74% of 31 marketing authorisations for an indication occurring in both in adults and children had no information for paediatric use included in their Summary of Product Characteristics at the time of the first marketing authorisations. Furthermore, 68% still have no paediatric information in their most recently updated Summary of Product Characteristics, at a median of 7 years later. Only 15 orphan drug designations (2%) pertained to a malignancy occurring specifically in children. This strongly supports the widely held view that at present the Orphan Drug Regulation does not facilitate drug development for childhood malignancy.

In conclusion, the hopes and expectations of parents of children with cancer and the paediatric oncology community have not been met by the Report. The landscape of paediatric oncology drug development must change to an approach driven by scientific data and the MOA of drugs and not be driven by a medicinal product's adult market and industry willingness to develop their drug for children with cancer. A major challenge is to develop a practical approach to the implementation of a MOA model without impacting the predictability of the scope of a PIP and leading companies to reconsider the overall product development. A further task is to understand, with more clarity, the reasons why the Orphan Drug Regulation is not benefitting children and adolescents with malignancies which do not occur in adults. We hope Paediatric Strategy Forums and the approach taken by the FDA in the implementation of the RACE for Children Act will inform policy decisions. We also hope this will result in greater trans-Atlantic regulatory alignment, which will be beneficial to many stakeholders.

We believe that a collaborative multi-stakeholder international approach will be the most profitable way forward to give children with cancer rapid access to potentially beneficial medicinal products. In addition, we urge the Commission to prioritise a more urgent review of the regulatory milieu than is currently planned (value of the Orphan Drug Regulation for children's cancers, suppression of Article 11b of the Paediatric Medicine Regulation). We firmly believe this to be pivotal in accelerating the desperately needed improvement in cure rates for poor prognosis childhood malignancies.

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