five (12%) of 41 patients being without disease progression at 12 months, it is necessary to improve the selection of patients that would benefit with nivolumab plus ipilimumab treatment or to combine different immune checkpoint inhibitors. Nivolumab plus ipilimumab can only be the starting point of immunotherapy for sarcoma.

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10-year report on the European Paediatric Regulation and its impact on new drugs for children’s cancers

In the paediatric oncology community, there was great hope and expectation that the European Commission report, State of Paediatric Medicines in the EU—10 years of the EU Paediatric Regulation,1 might suggest major alterations in the landscape of development of new drugs for children’s cancers. Have these expectations been met?

In the past 10 years, the European Union (EU) Paediatric Medicine Regulation (EC 1901/2006) has advanced drug development for paediatric oncology, but very few new medicines have been authorised for the treatment of 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 European Medicines Agency. One of the reasons for a waiver is if the indication does not occur in children.

To incentivise studies in children, companies with successfully completed PIPs are rewarded with a 6-month extension of their supplementary protection certificate for the investigational drug.

In 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, the pharmaceutical industry, patients, and regulatory agencies, among others.

We assessed the probable effect 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. 48 (54%) of these 89 drugs had a MOA warranting paediatric development. Two (2%) drugs were considered not to be relevant, and 16 (18%) required further data.5

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Supported by these analyses, we proposed a MOA-based approach with five initiatives: an aggregated database of paediatric biological tumour drug targets; a joint academic–pharmaceutical industry preclinical platform to analyse the activity of new drugs (Innovative Therapy for Children with Cancer Paediatric Preclinical Proof-of-Concept Platform [ITCC-P4]); paediatric strategy forums; molecular profiling of paediatric tumours at diagnosis and relapse; and 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. The first three of these approaches have been implemented: a database of targets has been created, and the ITCC-P4 has been funded as a project of Innovative Medicines Initiative 2 and is operational. Furthermore, there have been two paediatric strategy forums in 2017 on ALK inhibition and drug 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 has been substantial policy change, after the passing of the FDA Reauthorization of 2017 (Research to Accelerate Cures and Equity [RACE] for Children Act) by the US Congress on Aug 3, 2017. This Act states that “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 USA, there will soon be an operational MOA-based model for the development of oncology drugs for children.

Against this background, what are the conclusions of the State of Paediatric Medicines in the EU? The report shows that the benefits of the Regulation are dependent on companies’ adult product pipeline and influenced by revenue prospects in a specific market. When the adult market expectations overlap with paediatric therapeutic needs, children will sometimes profit directly—eg, by access to newer drugs for diseases such as acute myeloid leukaemia and certain sarcomas, which can cross the age divide. By contrast, for diseases that are unique to children, drug development depends on the strategic decision of a company to invest in this area independently of any ongoing adult programme. This approach 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.”

Furthermore, the report authors acknowledge that there have been many PIPs for drugs for children’s cancer, but few of these have been completed. The report also states that there is widespread use of the Regulation’s deferral system, which leads to delays in drug development for children, often until the market of an adult cancer indication is secured.

The authors of the report highlight the relevance of a MOA approach, but do not suggest any concrete proposals about how this could be implemented in the EU. They raise a concern that a MOA model could affect the predictability of the scope of a PIP and might lead companies to reconsider the overall product development. For paediatric oncology, the report states “a considerable number of new adult cancer products thrive on the stimulus provided by the Orphan Regulation, while this is not matched for paediatric cancers, albeit all qualify as rare in the sense of the Orphan Regulation. 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 effect of the Orphan and Paediatric Regulations in diseases that occur only in children, “therefore and before proposing any amendments, the Commission intends to take a closer look at the combined effects of the Orphan and Paediatric Regulation through a joined evaluation of those two legal instruments aimed at supporting medicine development in subpopulations of particular need.” The Commission’s further investigation of these two regulations aims to provide results by 2019, to allow the next Commission to make an informed decision about possible policy options. It will also allow the forthcoming results of the assessment of supplementary protection certificate to be taken into account. Unfortunately, this 2-year process is
likely to further delay optimisation of the regulatory environment to stimulate improvements in drug development for childhood cancer.

We reviewed 657 oncology orphan drug designations and found that 272 (41%) are related to malignant conditions occurring both in adults and children. However, 23 (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, 21 (68%) still have no paediatric information in their most recently updated summary of product characteristics, at a median of 7 years after authorisation. Only 15 (2%) orphan drug designations pertained to a malignancy occurring specifically in children. This finding 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 findings. The landscape of paediatric oncology drug development must change to an approach driven by scientific data and the MOA of drugs, and not by a drug’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 affecting 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 that do not occur in adults. We hope paediatric strategy forums and the approach taken by the US Food and Drug Administration in the implementation of the RACE for Children Act will inform policy decisions. We also hope this will result in greater transatlantic regulatory alignment, which will be beneficial to many stakeholders.

We believe that a collaborative, multi-stakeholder, international approach will be the most beneficial way forward to give children with cancer rapid access to potentially beneficial drugs. Additionally, we urge the Commission to prioritise a more urgent review of the regulatory milieu than is currently planned (eg, investigate the Orphan Drug Regulation for children’s cancers, suppress article 11b of the Paediatric Medicine Regulation). We firmly believe this approach will be pivotal in accelerating the much needed improvement in cure rates for childhood malignancies with poor prognosis.

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ADJP is retired.


7 US Congress. https://www.congress.gov/bill/115th-congress/house-bill/2430/text?q=%7B%22search%22%3A%5B%222%22%5D%22%22%3A%5B%22hr+2430%22%5D%22%7D&d=1H2A66BE74006394DC9EB492C9F8A1509C (accessed Jan 8, 2018).