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Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer

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Abstract Seven years after the launch of the European Paediatric Medicine Regulation, limited progress in paediatric oncology drug development remains a major concern amongst stakeholders – academics, industry, regulatory authorities, parents, patients and caregivers. Restricted increases in early phase paediatric oncology trials, legal requirements and

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Paediatric Investigation Plan
Precompetitive development
Long-term follow up

regulatory pressure to propose early Paediatric Investigation Plans (PIPs), missed opportunities to explore new drugs potentially relevant for paediatric malignancies, lack of innovative trial designs and no new incentives to develop drugs against specific paediatric targets are some unmet needs. Better access to new anti-cancer drugs for paediatric clinical studies and improved collaboration between stakeholders are essential. The Cancer Drug Development Forum (CDDF), previously Biotherapy Development Association (BDA), with Innovative Therapy for Children with Cancer Consortium (ITCC), European Society for Paediatric Oncology (SIOPE) and European Network for Cancer Research in Children and Adolescents (ENCCA) has created a unique Paediatric Oncology Platform, involving multiple stakeholders and the European Union (EU) Commission, with an urgent remit to improve paediatric oncology drug development. The Paediatric Oncology Platform proposes to recommend immediate changes in the implementation of the Regulation and set the framework for its 2017 revision; initiatives to incentivise drug development against specific paediatric oncology targets, and repositioning of drugs not developed in adults. Underpinning these changes is a strategy for mechanism of action and biology driven selection and prioritisation of potential paediatric indications rather than the current process based on adult cancer indications. Pre-competitive research and drug prioritisation, early portfolio evaluation, cross-industry cooperation and multi-compound/sponsor trials are being explored, from which guidance for innovative trial designs will be provided.

1. Introduction

Childhood and adolescent cancers remain a major cause of morbidity, mortality and social concern in Europe [1–3] with 3000 children and adolescents dying of cancer each year [4]. In the developed world, although 80% of children survive cancer, they may suffer long-term effects from their treatment [5] and approximately 20% of patients will die of their disease or of disease-related causes; as such paediatric cancer remains the number one non-accidental cause of death in children and adolescents [6]. Improvements to all standards of paediatric cancer care and a focus on incurable diseases are urgently needed, entailing fresh approaches to the many complex aspects of treating childhood cancers, including faster introduction of new medicines for children into front-line care, innovations in study design and drug development and collaboration between stakeholders. Additionally, as new drugs are introduced, it is imperative for childhood cancer survivors to have long-term follow up (LTFU) into adulthood to collect data on the later effects of childhood treatment for cancer [2].

The European Paediatric Regulation [7] provides the regulatory framework for drug development for children and adolescents with cancer. It aims to increase availability of authorised medicines for children through generation of safety and efficacy data and high-quality ethical paediatric clinical research, and to produce better information on paediatric medicines, in general. Overcoming off-label use by developing and making available new, age-appropriate paediatric medicines is also within the Regulation's remit.

The Paediatric Regulation stipulates that pharmaceutical companies propose and comply with a Paediatric Investigation Plan (PIP) before seeking marketing authorisation (MA) for a new medicine (or variation of an existing MA). Completed PIPs are rewarded with a six-month extension of the medicine's Supplementary Protection Certificate (SPC) or, in the case of orphan-designated medicines, a 2-year extension of the 10-year market exclusivity for the authorised indication.

Despite significant changes in paediatric oncology drug development in the years after the Regulation came into force in 2007 and an increase in the total number of PIPs filed, frustration remains amongst all stakeholders at the seemingly slow speed of progress [8]. The lack of a unified driving force to facilitate coherent actions for further change and progress has become apparent. A lack of increase in early phase paediatric oncology trials in Europe compared with the United States (US), growing regulatory requirement to propose PIPs early in drug development, missed opportunities to explore efficient drugs in development for adults that may be relevant for paediatric malignancies, lack of innovation in trial designs and limited incentives to develop drugs against specific paediatric targets continue to be areas of significant concern for paediatric drug developers across academia, industry, regulatory authorities, and importantly, amongst patients, parents and caregivers.

To address these concerns and promote progress, two-yearly Paediatric Oncology Workshops were initiated in 2011 by the Cancer Drug Development Forum (CDDF, previously the Biotherapy Development Association (BDA)) along with the European consortium for Innovative Therapies for Children with Cancer (ITCC), and the European Society for Paediatric Oncology (SIOP Europe) [1], within the framework of the European Network for Cancer Research in Children and Adolescents (ENCCA). The ITCC consortium was created in 2003 to develop early evaluation of new

oncology drugs [9] and ENCCA is a network of excellence awarded funding for 2011–2015, in the European 7th Framework Programme (FP), to structure and enhance collaboration in clinical and translational research in European paediatric oncology.

The 2011 BDA/CDDF Workshop identified sectors within paediatric oncology drug development for action and specific strategies to improve upon and speed drug development and despite methodological challenges, between 2011 and 2013 some improvements to paediatric cancer drug development were made. The second workshop in 2013 examined paediatric cancer drug development progress, or more specifically lack thereof, and sought input from all stakeholders on the means to enact needed changes. The need to create a Paediatric Oncology Platform to enable all stakeholders to work together to improve current implementation of the Regulation was made clear, as was the need to identify where changes may most usefully be made to the Regulation at the time of its review in 2017.

2. Landscape, needs and progress (2011–2013)

2.1. Regulation

Pharmaceutical companies are regulated by the legal framework Eudralex, a 10-volume collection of regulations governing medicinal products for public health needs in the EU. The Paediatric Regulation aims to make medicines for cancer and other diseases available in Europe for children [7]. The European Medicines Agency (EMA) operates within this framework. Securing authorisation for oncology drugs requires extensive assessment of data on quality, efficacy and safety. In oncology drug development, data are often not sufficiently robust and failure late in development is a particular risk due to early studies not being predictive and target populations not well identified. Such challenges are even greater for paediatric oncology medicine development because often less is known about these new medicines and their effects on paediatric cancer, both pre-clinically and in the clinic and rarely are exploratory studies performed in children before a clear benefit-risk relationship has been established in adults.

Within the EMA, the Paediatric Committee (PDCO) is responsible for agreement of PIPs proposed by the sponsoring pharmaceutical company. PIPs include comprehensive study plans aimed at generating age-appropriate safety and tolerability, pharmacokinetic (PK) and, potentially, efficacy data for MAs of medicines for specific indications in children. Each MA for an adult indication (e.g. treatment of breast cancer) requires an agreed PIP covering the same condition, and/or a waiver for clinical studies where there is no opportunity for a paediatric indication. Waivers can be granted on three specific grounds – the product is likely ineffective or unsafe, the condition or disease does not occur in children, or the product does not represent a significant benefit over existing treatment. As a result, the opportunity to study innovative anti-cancer medicines in children is difficult.

In 2012, the Commission reported that in general there had been improvement in the development process for paediatric medicines since 2007 [10]. However, this was not true for paediatric oncology where expectations for PIPs had not been met [8]; while the number of submitted PIPs had increased overall, successful completion had not always followed. Although the PDCO can review and agree to the original requirements of a PIP, modifications often follow as additional adult data are acquired during development, resulting in terminated development programmes, and modified PIPs. In part due to this there have been half as many modified PIPs as new PIPs. This again highlights the challenges faced in paediatric oncology drug development, which is perceived as dependent upon adult indications.

In addition, regulators are aware that the current Regulation does not yet fully cover the public health needs of paediatric oncology due to the mismatch between the conventional adult-centred drug development programmes and the urgent medical need in taxonomically unrelated paediatric malignancies. Work is ongoing to develop a more relevant framework for paediatric oncology PIPs based on a drug's mechanism of action (MoA) rather than the adult indication, particularly where a drug is used in adult oncology and where there is evidence for use in children with as yet unmet needs. Encouragingly several companies have already proposed such MoA driven PIPs on a voluntary basis.

Finally in 2011, the European Network of Paediatric Research at the EMA initiative (EnprEMA) was established to facilitate communication between academia and the EMA enabling paediatric groups to share knowledge and best practice. Enhanced communication between the EMA and the Federal Drug Agency (FDA) also contributed to better overall communications. There was simplification of some administrative regulatory requirements and a small increase in the number of PIPs in oncology, but the pace of change continues to be too slow.

2.2. Academia

While survival for childhood cancers has improved steadily since 1960, as of 2000 the decrease in mortality has reached a plateau. For children with poor-prognosis cancers resistant or refractory to conventional treatment, overall survival is less than 25%. High-risk leukaemias, high-risk neuroblastomas, metastatic sarcomas, high-grade gliomas and high-risk medulloblastomas are the most common paediatric cancers with poor outcomes [11–17]. Improvements in survival for children with these diseases have lagged behind other malignancies, and with

intensification of therapies, long-term complications have increased leading to chronic and disabling morbidities [18,19].

Despite successful development of molecularly targeted therapeutics in adults over the last decade, relatively few such studies have been completed in paediatric oncology, highlighting an unmet need in this area. Further progress in this field suggests clinical trials driven by biological hypotheses result in higher numbers of drugs reaching the bedside [20,21], but this has not yet translated into improvements within paediatric oncology drug development.

From 2007 to mid-2012, 45 PIPs were approved in oncology for the central nervous system (CNS), leukaemia, lymphoma, solid tumours and supportive care, but none have included the most aggressive of childhood cancers such as high-risk neuroblastoma [22]. This is because creation of PIPs has been driven by the relevant adult indication; regulatory obligations for paediatric development for a number of drugs with potential for childhood cancers were waived, as noted above, despite the fact that the MoA may have been shown to be biologically relevant in a specific paediatric cancer.

Since 2007 the number of drugs in early phase trials being run by the ITCC has grown from one in 2007 to 12 in 2013, with half the trials being conducted to comply with the regulatory requirements of a PIP [23–28]. The New Drug Development Strategy (NDDS) project run by ITCC and ENCCA continues to define strategies for specific malignancies. However, of 28 non-generic oncology drugs approved since 2007, of which 26 were potentially relevant for paediatric malignancies based on MoA, 50% of them were waived [22].

For the academic community, frustration continues in the lack of early access to new drugs for preclinical and early clinical trials, the difficulty of organising, funding and conducting academic-led trials, and the challenge of managing PIPs. A development programme in an adult disease should not be the only valid guide to paediatric oncology drug development, and paediatric development should instead clearly be guided by the biology of the malignancy and the MoA of the drug. Only then will true benefit again be able to be seen in paediatric cancer drug development.

2.3. Industry

As PIP requirements become more stringent, sponsoring pharmaceutical companies have invested more time and resource to develop and execute them; specifically because of the numerous PIP modifications noted above, this process is often long-term, and delivery of a successful PIP is often seen as ‘at risk’. Multiple PIPs in the same area of development, for example, within a similar diagnosis or tumour type may be required, and make recruitment to required clinical studies and subsequent successful PIP execution extremely difficult. There is also a lack of clarity on the procedure regarding the compliance check at the finalisation of the PIP. For small organisations, such as biotechnology companies and so-called ‘start-ups’, the increasing cost of paediatric development can be prohibitive despite the long-term incentives offered by the Paediatric Regulation, and the PIP opportunity is often unclear, or lost with these early phase compounds, as the ultimate fate of many molecules in development by biotechnology companies is unknown to their sponsor.

Additional, significant challenges are posed by discrepancies between US and European requirements, as well as by differences in timelines for paediatric drug development. Numerous delays have been identified around PIPs which, while a European legal requirement, have global implications. Although there are similar but not identical legal requirements in the United States, the mismatch between PDCO requirements, academic recommendations and US and EU agencies has led to considerable challenges for industry, where the drive to paediatric development may be rare or absent, and balance, greater flexibility of process and collaborative venture are essential to the success of a paediatric programme. Greater clarity, and more importantly synergy between legislative regulations may improve the ability of industry to deliver a singular, succinct paediatric oncology drug development plan to time and quality.

2.4. Parents, patients and patient advocates

For parents and patient advocates there are aspects of paediatric oncology drug development that are unpalatable and unacceptable. The lack of options through early phase trials for patients with relapsed malignancy and painfully slow progress in bringing new drugs into front-line therapy are very major concerns. Financial limitations within the pharmaceutical industry and regulatory hurdles within EMA are perceived as a hindrance to an increase in paediatric trials and a cause of major delays in the development of specific drugs for children. The disparity between US and EU paediatric drug development due to the lack of centralised funding in Europe and poor coordination between EMA and FDA on the authorisation process is an enormous frustration and leads, each year, to parents taking their children to the US for treatment that is unavailable in Europe; this is both an emotional and financial cost to families and a cause of inequality of treatment. Parents and patient advocates see paediatric drug development as a social responsibility and the perceived lack of drive for change and lack of flexibility in the system is a cause of frustration.

Meanwhile, there is recognition that patient advocacy groups could achieve more through better focussed collaboration in the field of lobbying regulators, sponsors, politicians and policy makers, and in fundraising. The

Creating Hope Act (2010), initiated in the United States of America (USA) by the mother of a child who did not survive cancer, provides a transferable incentive to sponsoring pharmaceutical companies – an FDA priority review voucher – and shows what is possible with directed partnership [29].

3. 2014–2017 focus

Until the opportunity comes in 2017 to revise the current Regulation, further developments and initiatives must take place within its confines and should act as a force for change to guide forthcoming modifications. Specific areas have been identified and are summarised in Table 1. Some of this work has already begun through the ITCC and ENCCA's New Drug Development Strategy (NDDS) programme, which is integrating basic, translational and clinical research into guidelines for drug development for each paediatric cancer and will provide expertise to regulators and pharmaceutical companies. Additionally, the NDDS disease focus groups bring together clinicians, researchers, statisticians, regulators, PDCO members and EMA's Paediatric Oncology Task Force, enabling academics and EMA/PDCO participants to share and address topics in oncology drug development.

4. The CDDF-ITCC-ENCCA-SIOPE Paediatric Oncology Platform

The Platform comprises four Working Groups each made up of members from all stakeholder groups

Table 1
Proposed initiatives and actions.

Improving early access to new anticancer drugs for children and adolescents in Europe

1. Improve access to compounds for preclinical testing and biological studies
2. Increase the number of drugs in early phase trials significantly
3. Consider running early phase trials before submitting a Paediatric Investigation Plan (PIP)
4. Consider accrual of adolescents in adult phase 1 and 2 trials when scientifically and medically relevant
5. Emulate the National Cancer Institute (NCI) clinical trial funding and programming model in Europe
6. Work to de-risk the perception of paediatric studies and create value in paediatric oncology
7. Simplify the process for initiation of a PIP proposal and enforce academic participation in this

Prioritising oncology compounds for development in children/adolescents with cancer

1. Develop a strategy for selection and prioritisation of drugs for paediatric development based on biology and mechanism of action rather than the current process based on adult cancer indications
2. Increase our understanding of molecular pathways and key drivers which are relevant for paediatric tumours
3. Set up disease focus groups: academic tumour groups must identify key contacts, review existing data on tumour biology and preclinical work, and define a strategy for each disease based on current treatment options
4. Consider paediatric oncology drug development as pre-competitive research
5. Set up early cross-portfolio evaluation, including academic investigators and paediatric oncology networks
6. Implement cross-pharmaceutical company discussion that will facilitate drug selection and prioritisation
7. Develop multi-compound, multi-company trials to speed up evaluation and spread risk and cost
8. Set up better incentives tailored to risks taken and commitments made by pharmaceutical companies, as well as for development of specific paediatric drugs

Facilitating cooperation and collaboration between all stakeholders

1. Achieve better academia-industry communication with improved trust and confidence. Academic groups to identify global leaders who will link with industry and have global harmonised opinions
2. Encourage four-party discussions and drug-prioritisation meetings
3. Broaden collaborative links between clinicians, scientists, European Medicines Agency (EMA)/Paediatric Committee (PDCO) and parent/patient organisations: the Cancer Drug Development Forum (CDDF)-Innovative Therapy for Children with Cancer Consortium (ITCC)-European Network for Cancer Research in Children and Adolescents (ENCCA)- European Society for Paediatric Oncology (SIOPE) Paediatric Oncology Platform
4. Set up an annual international working meeting with all stakeholders to update and share, address issues, propose solutions and elaborate action plans
5. Link with initiatives in North America and worldwide
6. Include the European Commission
7. Prepare the proposals for revision of the Paediatric Regulation in 2017

Setting-up long-term follow-up (LTFU) of children and adolescents exposed to new drugs

1. Set up LTFU that is patient-centred and performed in academic centres
2. Define LTFU so that data can be shared with regulatory authorities for continuous monitoring of benefit-risk
3. Build a joint programme and partnership between academia and industry
4. Use the concept of Survivorship Passport and empower survivors as partners of LTFU research
5. Implement LTFU on extension studies, with post-marketing surveillance and risk management plans
6. Perform large, joint – academic and industry – randomised trials and transfer LTFU to sustainable academic platforms
7. Consider cross-pharmaceutical company initiatives

– academia, industry, regulators and parent/patient advocates – and led by a stakeholder appropriate to the specific priority of that group:

4.1. MoA and biology-driven drug development within the current regulation

Academia led: To define a strategy and process for the implementation of MoA and biology-driven drug development and deliver precision medicine within the current regulation; (i.e. to drive the inclusion of patients into early drug trials through molecular profiling of their tumour).

4.2. Compound prioritisation across industry

Industry led: To address prioritisation of drugs within pipelines across companies (especially where several companies are developing drugs against the same target) and define how best to implement multi-compound/multi-company trials.

4.3. Innovative design and methodology for drug development

Including better extrapolation from adult data – EMA and PDCO led: To propose methodology guidance to accelerate paediatric drug development with consideration of current challenges: drugs used at their optimal biological dose; use of biomarkers; the challenge of the extreme rarity of paediatric patients with a biomarker-defined malignancy; and concomitant evaluation of efficacy and toxicity.

4.4. New incentives for specific paediatric drugs and drug repositioning

Parents/patient advocate led: To propose new EU regulatory initiatives to better incentivise drug development for life-threatening paediatric diseases; e.g. oncology drugs against specific paediatric biological targets (e.g. N-MYC in neuroblastoma) or drugs failing in adults to be repositioned for paediatric diseases.

The CDDF-ITCC-ENCCA-SIOPE Paediatric Oncology Platform will meet annually to monitor progress.

5. Conclusion

The CDDF-ITCC-ENCCA-SIOPE Paediatric Oncology Platform, a unique collaboration of academia, industry, patient advocates and regulatory authorities, has been formed to harness the energies of these stakeholder groups for their common purpose and most importantly to provide the drive for change in paediatric oncology drug development. The goal is to rapidly and efficiently evaluate and prioritise new anti-cancer drugs in children with cancer and to advance those with promise quickly into front-line therapy. For now this will be carried out within the confines of the current European Paediatric Regulation, but with a view to providing the framework for essential revisions to the Regulation in 2017. By strengthening cooperation through understanding and working with the problems faced by each stakeholder group, and through a determination to work cooperatively for the future of children with cancer, the Platform aims to achieve concrete results in paediatric oncology drug development.

Conflict of interest statement

None declared.

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