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Can a multi-stakeholder prioritisation structure support regulatory decision making? A review of paediatric oncology strategy forums reflecting on challenges and opportunities of this concept

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Abstract
Timely and successful drug development for rare cancer populations, such as paediatric oncology requires consolidated efforts in the spirit of shared responsibility. In order to advance tailored development efforts, the concept of multi-stakeholder Strategy Forum involving industry, academia, patient organisations and regulators has been developed.
We review the first five paediatric oncology Strategy Forums co-organised by the European Medicines Agency between 2017 and 2020, reflecting on the outcomes and the evolution of the concept over time and providing an outline of how a 'safe space' for multi-stakeholder engagement facilitated by regulators could be of potential value beyond paediatric oncology drug development.

Background:
Regulatory requirements introduced in the past 10 years have significantly shaped paediatric medicines development. This has led to a growing paediatric research and development infrastructure within the pharmaceutical industry, as well as an increased understanding of paediatric pharmacology, helping to define endpoints as well as methodologies of study design — such as extrapolation. This aims at translating into more focused paediatric medicinal developments and subsequent enhanced robust evidence generation.
These ongoing positive developments are well recognised. There is, however, still a high unmet medical need in various domains of paediatrics, including oncology, with only limited therapeutic advances made in the past 10 years. This holds true across the products’ research and development lifecycle, with delayed paediatric authorisations and a considerable global delay in access to novel therapies for children. The scientific, regulatory and operational complexity behind global drug development in rare cancers, such as paediatric malignancies is acknowledged: this relates in part to challenges with comparative evidence generation and timely completion of competing development programs in small populations. Yet it remains a public health interest to improve timely access to innovative therapies for patients with unmet medical needs, making best use of the existing regulatory frameworks and tools. Timely and successful developments depend critically on the principle of shared responsibilities among involved stakeholders, since each holds a discrete but synergistic role in the decision-making process of moving forward fit for purpose developments in a timely manner. With this in mind, the concept of a multi-stakeholder paediatric oncology Strategy Forum was introduced, defined and established in 2017 by the European Medicines Agency (EMA) and ACCELERATE (multi-stakeholder paediatric oncology platform for drug development). It is covered by the EMA framework of stakeholder engagement and provides an opportunity for transparent scientific discussion on topics of relevance to address unmet medical needs, in a pre-competitive space, involving all relevant stakeholders (patient advocates, clinicians/investigators, academic scientists, biotechnology/pharmaceutical companies and regulators – including EMAs committees, such as Paediatric Committee [PDCO], Committee for Medicinal Products...
for Human Use (CHMP), Pharmacovigilance Risk Assessment Committee (PRAC), Committee for Orphan Medicinal Products (COMP), CHMPs Scientific Advice Working Party as well as from the Food and Drug Administration (FDA)). The aim is to share information and priorities on key scientific issues that can inform subsequent strategic decision making, separately by each of the participating stakeholders, at the different steps of the product development life cycle, is expected to help in the development of paediatric products with focus and with enhanced feasibility and sustainability; as mandated by the Paediatric Regulation. The advent of precision medicine, associated with increasing fragmentation of already rare disease entities, underscores even more the need for such Forums, ensuring that patients with rare tumour types benefit timely from the fast-paced R&D environment in oncology. In this context successful commercial developments indeed depend critically on collaborative support from the academic community, including insights on feasibility, unmet need and optimisation of study design. The Forums provide validation of this input on a level playing field among competitors. All this exemplifies the EMAs’ mission to support innovation and timely access to novel treatments.

This article reviews the first five oncology Strategy Forums organised between 2017 and 2020. We reflect on the outcomes and the evolution of the concept over time and provide an outline of how a ‘safe space’ for multi-stakeholder engagement facilitated by the regulatory network could be of potential value beyond paediatric oncology drug development.

Framework, outcomes and evolution of the Paediatric Oncology Strategy Forum

Framework

The following principles were deemed critical to the concept of the Strategy Forums, with each stakeholder bringing a unique set of expertise and perspectives to the discussion: 1) Ensuring highest quality of scientific discussions through the involvement of leading academic experts in the field; 2) Participation of pharmaceutical industry based on expression of interest and willingness to actively contribute by presenting internal data of interest to the specific topic; 3) Ensuring focus on unmet needs by participation of parents and patient representatives; 4) Participation of regulators as active but neutral observers and free of regulatory decision making. This means that the role of the Agency is that of an observer during the discussion. Individual EMA members can of course contribute to the discussions. The forums, however, are meant to discuss mainly scientific issues and, similarly, the forums’ conclusions and consensus are intended to be based on solid scientific grounds.

In this role, the regulatory network is in a unique position to provide a sheltered forum that fosters transparent and data-driven pre-competitive interactions between all relevant stakeholders helping to share and learn up-to-date scientific information. The summaries of each Strategic Forum are published on the ACCELERATE and EMA website after the events.

The EMA is involved in the development of the Strategy Forums through active participation at the program committee which is tasked ranging from contributions to the preparation of the agenda, selection of appropriate speakers and invitation of participants. Through the involvement in the Steering committee of ACCELERATE the EMA is also part in the decision making on topic selection for upcoming Forums.

Summary outcomes and evolution

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A total of five Paediatric Strategy Forums were held between January 2017 and January 2020. The first Forum was a pilot and was hosted by the European Medicines Agency (EMA). The topic involved a discussion of anaplastic lymphoma kinase (ALK) inhibition in paediatric malignancies and covered six different products from five pharmaceutical partners. It demonstrated that the concept of the Paediatric Strategy Forum can be supported by all participating stakeholders. The feasibility and potential to catalyse conclusions which are relevant for paediatric cancer drug development, such as submission of voluntary Paediatric Investigation Plan (PIP) application, e.g., for brigatinib [EMA decision P/0350/2018] and Crizotinib with well-known activity in children with ALK-positive anaplastic large cell lymphoma and unresectable or relapsed/refractory ALK-positive inflammatory myofibroblastic tumours.

Following the first pilot, a second Forum dedicated to discussing development efforts in childhood mature B-cell malignancies, a specific and challenging disease group with numerous products under development was organised. Although there is good prognosis in children with newly diagnosed disease, a high unmet medical need is recognised among relapsed/refractory patients. Very few of these patients are globally available for enrolment in early clinical trials each year, while the differences between the disease in children and adults necessitate specific paediatric studies. As there are now many novel agents available in the pharmaceutical industry’s pipelines, the challenge here was to explore to which extent an agreement could be reached to focus development efforts for the most promising products with the most robust scientific rational. This second meeting took place on November 2017 and elicited increased interest from industry with 14 companies participating, discussing 20 different products. The Forum developed a consensus, formulated by scientists, academic experts and clinicians regarding the type of medicinal products which are, based on scientific rationale, considered to have the greatest probability of being beneficial in patients with relapsed disease. It was also agreed that there was a need to develop an overarching clinical trials strategy to allow all those products of high interest to be evaluated in a timely fashion. An international working group has been formed to develop a global industry-supported academic-sponsored study with compounds from different pharmaceutical companies using a master protocol. This underscores the principle of international collaboration involving multiple companies which is generally advisable to efficiently progress development in rare cancer types.

The second Forum successfully showed that focused scientific discussions conducted within a ‘safe space’ facilitated by the regulators, is able to produce consensus based on scientific justifications amongst clinicians, industry and patients/parents on prioritisation of different classes of products. The third Forum, held in September 2018, was on the topic of immune checkpoint inhibitor combinations in paediatric malignancies. The topic choice was driven by the success of immune checkpoint inhibition in adult malignancies not mirrored in paediatric malignancies. The objective was to consider opportunities for paediatric development in which checkpoint inhibitors are used in combination with other products to allow also children to benefit from this novel class of products. A total of 20 products from 16 companies were discussed, again highlighting the increasing recognition of pharmaceutical companies on the value of multi-stakeholder engagement. The Forum catalysed a discussion on how to best justify development efforts based on existing scientific evidence; to focus on combination therapies and to utilise exploratory proof of concept protocols, including drugs from...
multiple companies. It also concluded on the need for an international inter-company registry of paediatric specific early and late adverse effects of immunotherapies which is currently in the process of being set up 9.

The fourth Forum on medicinal product development for acute myeloid leukaemia (AML) was the first with the Food and Drug Administration (FDA) contributing to the organisation, recognising that drug development in rare diseases, such as paediatric oncology is only successful when approached globally. It was held in April 2019 and 26 products from 18 companies were discussed 10. The fourth edition highlighted the challenge to address a crowded R&D space.

Here again a consensus was achieved, agreed by all participants, allowing to focus development efforts to those products considered of high priority based on available scientific evidence. In addition, the Forum recommended to set-up a master protocol structure globally to allow drug evaluation of multiple treatment strategies within the same overall trial structure, intended for signal seeking in the small population of relapse/refractory AML 11. The master protocol is planned to be academically sponsored, industry supported, with products from different pharmaceutical companies and different mechanisms of action, using an adaptive design and conducted with ‘intent to file,’ meaning collecting data that can be reliably utilised for regulatory submissions.

Recognising that scientific evaluation is continuous, it became clear that a Strategy Forum is only an initial catalyst; in order for the concept to be sustainable and able to deliver actionable consensus statements, discussions need to continue beyond the Forum. Such follow-up activities were implemented for the first time after this Forum: internationally recognised academic experts in AML and clinicians, together with pharmaceutical companies with ongoing development efforts, held a follow-up meeting to discuss product specific prioritisations for FLT3 inhibitors and CD123 antibodies, identified as classes of products with highest interest in paediatric AML 12. The Forum showcased that it is possible to agree on refining strategies of already ongoing development efforts of products from different companies within a class. The value of the follow-up activities facilitating regulatory decision-making builds on the necessity to choose which products to move into early (and full) development, given the rarity of paediatric malignancies. But prioritisation decisions cannot be made by the regulators. These follow-up activities yield statements by investigators and companies, usually in consensus, on which products to move forward into clinical development and in which order. This can inform regulatory decision making for instance at the time of paediatric investigation plan submission.

The objective of the fifth Forum was to explore if multi-stakeholder engagement allows facilitation of early stage strategic planning of paediatric oncology developments, also driven by recent regulatory changes in the US 13. The topic was on epigenetic modifiers in paediatric malignancies, identified as an area of high scientific interest within the oncology community in general, hence giving stakeholders the platform to define the landscape. The Forum was held in the USA in January 2020 and 17 products from 11 different companies were discussed. Consensus was achieved on a list of priority molecular targets and a follow-up meeting for the class of BET-inhibitors was agreed, similar to one following the AML Forum 14.
In order for the topic of the Forums to continue reflecting the evolving needs of all relevant stakeholders, future topics will be chosen through stakeholder consultations (i.e., 6th Strategy Forum will be on the topic of CAR-T cell development).

Support to decision making for development of oncology products in children in the context of existing regulatory frameworks

From the onset it has been fundamental to clearly define the role of the regulators within the concept of multi-stakeholder engagement using the following guiding principles: 1) close initial involvement at the design stage of the Strategy Forum concept to ensure full compatibility with the existing legal regulatory frameworks; 2) provision of a ‘safe space’ that fosters transparency and instils accountability into the discussions; 3) no regulatory decisions made at the Strategy Forums and no regulatory advice provided; 4) a role of observer during the actual discussions, asking clarifications as needed; 5) ensuring equal opportunity of all relevant stakeholders to participate, even at different stages of individual product development; 6) provide general information on regulatory requirements relevant to the discussions; 7) remind the stakeholders of the expectation to continue the process by focused follow-up meetings. At these follow-up meetings regulators are not actively involved, but the outcomes are noted and expected to be reflected in subsequent product-specific regulatory procedures. Regulatory decisions continue to be made within the legal frameworks given, such as the Paediatric Regulation. These decisions will always depend on the evidence submitted by applicants. Yet, in our role of enablers of innovation, a consensus agreed among the relevant stakeholders (academic community, industry partners and parents and patient representatives), based on scientific justifications, outlining why certain product developments should be prioritised over others, why product development should focus on certain populations, or in which population a clinically meaningful benefit is most likely to be achieved, represents an invaluable perspective that should be taken into account during regulatory procedures.

Conclusion and future vision beyond paediatrics

This multi-stakeholder engagement supported by the Paediatric Oncology Strategy Forums has proven to be able to catalyse prioritisation discussions. It ensures that all voices are heard early in the process, including those of patients and parents. It has shown to be able to help providing clarity on prioritisation efforts retrospectively and most importantly prospectively at an early stage of evidence generation. The growing enthusiasm for this concept underscores the expectation that it can contribute to a more efficient, focused and sustainable R&D space where product development and robust evidence generation can be achieved more quickly.

We suggest that the concept of Strategy Forums has the potential to be of value beyond paediatric oncology. With the paradigm shift towards histology independent developments in oncology, driven by the advances in precision medicines, patient populations will become more fragmented than ever. Yet product pipelines are full. With this comes the necessity to carefully define the right target population, to agree among stakeholders on the best approach to generating pivotal evidence, potentially even beyond randomised controlled trials; which endpoints to use, acknowledging the importance of...
incorporating also the payers’ perspective. The regulatory network is committed to fostering innovation
globally aiming for patients to get timely access to efficacious and safe medicines. While necessary for
progress, all of these strategic aspects cannot be disentangled successfully in a timely manner in
isolation or on a product-by-product basis or sequentially. This leads to delays in achieving a common
understanding of the challenges of product development for small populations and a fragmented
approach to developing solutions. With the experience accumulated from five successful paediatric
oncology Strategy Forums, it is now enticing to explore if a similar concept can be applied to other
equally challenging, but more economically driven domains of cancer medicines development, where
pre-competitive engagement might be similarly beneficial, but possibly with barriers related to the
competitiveness of the market more difficult to overcome.

The Strategy Forums in paediatric oncology have shown that such efforts are possible, are of benefit to
all stakeholders, can deliver tangible results and accelerate innovation based on the principle of shared
responsibility. This blue-print has been recognised to be of general value for paediatric drug
development and is of potentially also for other parts of the global oncology community.

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