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European regulatory strategy for supporting childhood cancer therapy developments

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Abstract ***Introduction:*** Regulatory decisions on paediatric investigation plans (PIPs) aim at making effective and safe medicines timely available for children with high unmet medical need. At the same time, scientific knowledge progresses continuously leading frequently to the identification of new molecular targets in the therapeutic area of oncology. This, together with further efforts to optimise next generation medicines, results in novel innovative products in development pipelines. In the context of global regulatory development requirements for these growing pipelines of innovative products (e.g. US RACE for children Act), it is an increasing challenge to complete development efforts in paediatric oncology, a therapeutic area of rare and life-threatening diseases with high unmet needs.

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Objective: Regulators recognise feasibility challenges of the regulatory obligations in this context. Here, we explain the EU regulatory decision making strategy applied to paediatric oncology, which aims fostering evidence generation to support developments based on needs and robust science. Because there is a plethora of products under development within given classes of or within cancer types, priorities need to be identified and updated as evidence evolves. This also includes identifying the need for third or fourth generation products to secure focused and accelerated drug development.

Conclusion: An agreed PIP, as a plan, is a living document which can be modified in light of new evidence. For this to be successful, input from the various relevant stakeholders, i.e. patients/parents, clinicians and investigators is required. To efficiently obtain this input, the EMA is co-organising with ACCELERATE oncology stakeholder engagement platform meetings.

1. Introduction

The overall goal of paediatric regulatory obligations and rewards, as mandated by the EU Paediatric Regulation (Regulation (EC) No 1901/2006), is to stimulate timely development of better medicines for children based on ethical research of high quality and to ultimately increase the availability of appropriately authorised medicines through paediatric investigation plans (PIPs) agreed by the European Medicines Agency's Paediatric Committee (PDCO) [1]. However, achieving this objective is sometimes challenging: regulators and medicine developers must take into account different levels of evidence in view of the unmet therapeutic needs of paediatric patients. This has become particularly evident in the therapeutic area of paediatric oncology. Despite growing innovations translating into increasing developments in adult oncology, there is concern for the scarcity of authorised medicines with innovative mechanisms of action being available to children with cancer. This is understood to be based on challenges in conducting timely and feasible developments, i.e. to identify the most promising agents, within same in class and beyond, for development in small populations, appreciating feasibility constrains, so that evidence can be generated in a timely manner and be sufficiently robust for benefit-risk assessment for marketing authorisation. It has been recognised that there is a higher chance of addressing these challenges if all relevant stakeholders are involved, for example, in a multi stakeholder environment. The aim of this manuscript is to elaborate on the evidence based regulatory decision strategy. This includes supporting innovative methodologies, such as platform trials, but also prioritisation discussions led by clinicians and clinical researchers in view of facilitating timely availability of promising novel therapies for children with cancer.

1.1. The initial paediatric investigation plan (PIP)

The initial PIP decision, individually assessed on its own merit, includes the studies expected to be necessary to obtain marketing authorisation in children. A PIP may include not only clinical, but also non-clinical and/or quality studies in case an age appropriate formulation development is needed. As this constitutes an early plan for such development, it means accepting and mitigating levels of uncertainty on the actual potential of the product for children. This is a general challenge for devising a development plan and implies that the pharmaceutical landscape, public health needs and scientific insights and achievements are considered at an early stage of regulatory interaction. Therefore, inevitably, if the product is promising, the outcome of the first regulatory interaction will most likely reflect ambitious development goals framed in a development plan able to assess benefit-risk in a context of high or highest unmet needs. This may hence include a plan for development in a front line setting where the need and consequential benefit of new innovative drugs is expected highest. At the same time, when paediatric preclinical proof of concept data may not be available at the initial PIP discussion or are even impossible to generate, the PDCO must take regulatory decisions based on very limited data.

When this is the case, some studies, such as for development in first relapse or front line setting might be outlined only at a high level awaiting more supportive evidence. While several PIPs could be agreed for same in class products or within the same condition, it should be considered that this increases the chances of getting at least one medicine authorised and reimbursed for children in view of the high attrition rate at various stages of development, especially in oncology. For the same reason, granting a waiver at an early stage, without sufficient data supporting such decision, is not considered appropriate. Requests for product-specific waivers have to be based on one of the three existing legal grounds, i.e. likely lack of safety or efficacy, disease or condition not existing in a specified age-subset and lack of significant therapeutic benefit, and need to be supported by sound evidence from (non-)clinical data with the individual compound or from other compounds with a similar mode of action. If strong data are not available, regulators are likely to take a waiver averse approach, with sound

evidence needed to fully waive a development at an early stage. This avoids premature exclusion of paediatric development of potentially effective products and ensures data generation to support developments for a potential best-in-class product in children.

1.2. The PIP life cycle

All stakeholders, including the regulators, acknowledge that evidence evolves continuously. This may include changing priorities for drug development after an initial PIP decision has been adopted. Regulatory decision-making should be seen in the context of the product development life cycle, with regulatory interactions aiming at providing continuous support to achieve the goal of successful and timely drug development leading to a marketing authorisation. The EU Paediatric Regulation allows modifying PIPs so that emerging data are taken into account, which could change the expected safety and/or efficacy of the product in children [1]. An agreed PIP, as a plan, is a 'living' document and regulators hence acknowledge that data are accrued on products continuously which could justify modifications of the development plan or could result in changing the product's expected significant therapeutic benefit over time. When objectives of an early phase study for example are not met, further development of the product in a pivotal setting should be questioned. A PIP decision reflects the outline to generate sufficiently robust evidence of the efficacy and safety of the medicinal product. In case of limited patient availability, such evidence can be generated as part of an academic master protocol for a given condition, for example, the PedAL/EUPAL initiative in acute myeloid leukaemia (AML) [2], or GloBNHL for mature B cell malignancies [3]. The latter are platform trials led by academia for treatment of children with acute myeloid leukaemia and relapsed/refractory mature B cell malignancies, respectively, evaluating several highly promising classes of products from different companies. They are collaborative initiatives which aim at producing data that can be used to support marketing authorisation applications.

1.3. Regulatory decision making based on emerging evidence

Experience shows that a regulatory strategy based on emerging evidence, is best able to achieve the outlined objective of ultimately increasing the availability of paediatric medicines, it also empowers clinical investigators to lead discussions on prioritisation among multiple, sometimes competing, requests for clinical studies triggered by regulatory obligations. This approach is compatible with companies' proactive strategies involving repeated cycles of prioritisation of development opportunities to be revisited in collaboration with clinicians. Instead of 'competitive' developments, the 'collaborative' strategy can ensure to collect the needed data for marketing authorisation of innovative active selected compounds in paediatric cancer at earlier stage of development and ultimately their availability for the patients. Such regulatory strategy has shown to be successful: one clear example is the impact of the conclusions of multi-stakeholder discussions at the Paediatric Strategy Forums organised by ACCELERATE in collaboration with the EMA and participation of the FDA between patients/parents, academia and industry on product classes for the treatment of paediatric mature B cell malignancies, which eventually led to the modification and closure of already agreed PIPs for products considered at that stage to be of limited benefit to children [3]. At the same time this approach also ensures that the patients' voice is heard in this context at an early stage. As with any supportive scientific evidence the peer-review published scientific outcome of these forums can be taken into account by PDCO for the evaluation of new emerging evidence if reflected in PIP submissions (new initial PIP or modification). This has been for example the case for development plans for treatment of mature B cell malignancies, based on the reported science-based prioritisation process involving collaborative multistakeholder approach by patients and parents, academia, investigators and industry. This strategy relies on dedicated and a commitment to meaningful and self-standing yet transparent (to regulators) collaborations between industry and academia (ACCELERATE in this case [4]).

Alternative approaches to the strategy above, such as involving an early hypothesis-based selection of certain 'promising' products by differential regulatory obligations is expected to be less effective. The progress of science is indeed such that scientific evidence generation may lead to evolving insights and prompt modification of hypotheses and expectations. Valuable candidates could therefore be discarded prematurely based on very limited data. This could in turn lead to missing opportunities to address unmet needs that could not withstand public scrutiny. It is more scientifically justifiable to support optimal development efforts based on scientific data, leading to similar products being initially subjected to equal obligations. It is also not expected that all agreed development plans will necessarily be completed, let alone that all products will reach the market. As development progresses, using pre-specified decision points, obligations may be modified, reduced and even lifted later on, based on the accumulating evidence. However, importantly, emerging promising data should be used to further fill the gaps in the development program identified/outlined in the initially agreed higher level PIP.

The alternative approach of 'delaying' the agreement of regulatory development obligations until supporting evidence becomes available, i.e. only submitting initial PIP applications when comprehensive supportive non-clinical and adult clinical data become available, is even more unlikely to yield success in the sense of timely access to the medicine for children, and for this reason is also

clearly not supported by the Paediatric Regulation. History has shown that there is little incentive for such late evidence generation in paediatrics, even in a context of high unmet need. There are examples where despite a clear unmet medical need and strong supportive evidence, a PIP supporting a paediatric marketing authorisation application was submitted years after the adult marketing authorisation was granted.

For this regulatory decision making based on emerging evidence to be successful, there is the need for collaboration among all stakeholders fostering an environment of evolving evidence and needs. Importantly, such a strategy builds on the commitment for continuous cooperation and data sharing, with a drive for agreement on identifying priorities, and collaboration particularly among different academic groups globally, between patients, parents, academia and industry. This requires dedicated and unbiased academic leadership and a level of mutual trust. The ACCELERATE multi-stakeholder platform in paediatric oncology is an example for such a successful approach [5–9].

1.4. Practical considerations

What does this mean in practice? For paediatric oncology it means that initially agreed paediatric development plans in an agreed population and condition will be maintained until further evidence becomes available, contextualised through discussions at established multi-stakeholder platforms catalysing for example prioritisation of certain development efforts, like which product to move into development in an identified target population first in case of multiple same in class products. In case of high-level agreements, like PIP studies for front line development, these are expected to be modified and aligned with priorities, when adequate scientific evidence becomes available and is presented as a basis for regulatory decision making. This will take into account emerging evidence in the context of an evolving R&D landscape and potentially changing needs. When several PIPs exist for a given condition, the development plans will be maintained and a focus will be on the evidence related to potentially added significant therapeutic benefit a product might offer not only over existing treatments, but also over novel products in development.

Development discussions should focus on the paediatric target population with the highest unmet medical need, appreciating that the usual starting point of development in oncology—the last line relapsed/refractory setting—should only be seen as an intermediate development step to also address the unmet needs in earlier lines of therapies (e.g. first relapse, or front line therapy).

What exactly could be considered to potentially confer a significant therapeutic benefit to the identified target population in high need? It could be, for example, the product's route of administration, availability of a suitable age-appropriate formulation and/or an improved dosing-regimen. Clinically, it could be the ability to target new mechanisms relevant for tumour growth, improved activity over standard of care shown by either extrapolation of adult data (if biologically relevant), non-clinical data or even clinical data in children. Benefit could be also conferred by better target organ penetration or the ability to overcome clinically relevant resistance. In terms of safety, it could be the ability of the product to be suitable for combination developments or evidence of less short-term or long-term toxicities as compared to currently used therapies (see also respective reflections presented at Pediatric Oncology Subcommittee of the Oncologic Drug Advisory Committee Meeting in May 2022 [10]. The type and strength of evidence required to prioritise or de-prioritise a product will greatly depend on the development context. Early engagement with stakeholders to discuss the points above is expected to accelerate completion of the paediatric program.

Collectively agreed evidence-based conclusions of overarching transparent reviews of a specific area of development, when shared with and agreed by regulators, can support modifications of agreed development plans.

The agreed content of a PIP will need to be fit for purpose, allowing for evidence generation and a focus on scientific dialogue when interacting with the regulators, rather than administration.

This approach to allow modifications on development efforts based on emerging evidence is different from the well-established strategy of early pipeline prioritisations, as commonly done by pharmaceutical companies. In the latter, the company's driver, economically and operationally, is to channel resources, mitigate failure and enhance success at an early stage. However, what needs to be channelled in paediatric drug development are not only company resources but also mindful approaches towards maximising the usefulness of data obtained from the limited number of patients available to be able to address questions related to unmet medical needs. This approach makes it clear that an agreed paediatric development as part of a PIP is neither a protocol, nor an isolated regulatory requirement, but a plan that, in accordance with the Paediatric Regulation, can be modified in light of the emerging scientific evidence. Bringing all development efforts together into one arena allows for timely evidence-based and focused discussions on priorities (see also for overall summary).

International regulatory collaboration to support global development efforts in paediatric oncology, particularly with the US Food and Drug Administration (FDA) is well established [11]. Experience so far has shown that the implementation of the US RACE for Children Act, complementary to the European Paediatric Regulation, is not a barrier towards successful application of our described regulatory strategy, as long as the principles of transparency and simultaneous regulatory submissions are followed [12].

2. Conclusion

Overall, the described approach to base decision making on emerging evidence currently taken by regulators takes into consideration evolving scientific knowledge and unmet needs. This is to ensure that the overall objective is achieved collectively in the interest of the patients. As showcased in paediatric oncology, it is an approach that can be successful. However, it requires willingness to participate to and support of science driven interactions, to discuss and implement innovative trial designs, like the platform trials mentioned above, transparency, early and close collaboration between all stakeholders. But also supporting infrastructures which should reach beyond well-established cooperative groups and academic networks. Finally, of course, it relies on a regulatory responsibility to listen and critically assess any conclusion of prioritisation outcome based on its scientific robustness and rigour.

This is an equally applicable concept able to support paediatric development across all therapeutic areas with high unmet needs. We believe that the described strategy is a conceptual consideration to success for any future revised regulatory framework, within which regulators are eager to foster innovation.

Author contribution

All authors: Conceptualization. **DK, KN, GF, FL**: Writing Original Draft. **All authors:** Writing – Review and Editing.

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