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Common Commentary - EMA/FDA

Common issues requested for discussion by the respective agency (EMA/PDCO and FDA) concerning paediatric oncology development plans (Paediatric Investigation Plans [PIPs] and initial Pediatric Study Plans [iPSPs])

Background

Cluster calls have provided an opportunity for regulatory agencies to engage in high-level scientific discussions of paediatric development plans of new drugs and are able to inform regulatory decision making of each agency. Regulatory agency alignment on paediatric development plans is especially critical given the demand for international clinical trial collaboration necessitated by small study populations in rare diseases such as childhood cancer. Acceleration of paediatric development plans for novel anti-cancer agents can be greatly facilitated by transparency of industry sponsors on their individual plans to fulfil EU and US requirements and by simultaneous submission of iPSPs and PIPs to the FDA and EMA, respectively (Reaman G et al; JCO 2020). Attention to global product development requires consideration of additional regulatory agencies outside of the U.S. and EU.

This document describes key issues which are commonly requested by the respective regulatory agency to be further discussed by the sponsor. Adequately addressing these issues upfront will permit focused discussions during cluster calls, allowing for coordination of global development plans.

Administrative and Product information

Please add all interactions you have had with the FDA and with EU regulatory agencies concerning the paediatric development; indicate if you wish to request a common commentary.

Consider approaching other international regulatory agencies, such as PMDA, HC, and TGA in recognition of the necessary global development program approach to new treatments for children with cancer.

Overall development of the medicinal product

EMA position for PIP applications

Discuss the unique features of your product. Why is it considered to be able to address current and perhaps future unmet medical needs based on its mechanism of action in the targeted condition. Based on the mechanism of action of the medicinal product, discuss where the product may ultimately best be positioned in the therapeutic armamentarium, including line of therapy and potential use in combination. If considered for

See websites for contact details

U.S. Food and Drug Administration: www.fda.gov

European Medicines Agency: www.ema.europa.eu



development solely or primarily in the relapsed/refractory setting, elaborate on why it does not have a potential for significant therapeutic benefit in the front-line setting.

Reference to all relevant guidelines should be made as necessary.

Overall, it is reminded that the PIPs objective is to generate data for a full paediatric development, i.e. the studies needed to assess the benefit-risk in the target population.

FDA position for iPSP applications

Detail the pediatric incidence of the clinical indication for which the drug product is being developed and whether there is a rationale for the potential use of extrapolation from adults to children. More importantly, consider the molecular mechanism of action of the drug product and the specific target to which the product is directed. If that target is relevant to the growth or progression of one or more cancers that occur in the pediatric age group, discuss plans for early study(ies) of the product in children to provide data on dose, tolerability, and signal of activity or justify why such studies or results of studies should be deferred or waived and in which specific pediatric age groups. Description of additional studies both non-clinical and clinical that warrant discussion and comment in the context of a more definitive development plan may also be included. Generally, staggered age enrolment is not recommended unless there are specific toxicity concerns for the youngest age groups of children as supported by clinical experience in adults or juvenile toxicity studies which are not generally required or recommended without specific concerns that the mechanism of action of the product may adversely impact specific organ or system development.

Waiver discussions:

EMA position for PIP applications

The default position by the PDCO is that no age specific waiver is needed, unless sufficient justifications are presented in support of one of the three existing waiver grounds for a lower age cut off.

The approach taken by the PDCO is that if the disease does occur even in very young patients with an acknowledged unmet medical need and/or if one can extrapolate based on disease similarity and there are no specific safety concerns, there should be no need for a lower waiver cut off age, particularly if no minimum number of patients to be recruited are specified for the lowest age subset.

FDA position for iPSP applications

Planned waivers for drug products that are the subject of supplemental applications can be considered if the indication does not or only rarely occurs in children making studies impossible or highly impracticable or if the drug poses significant toxicity concerns or is unlikely to be used in children. Plans for age specific waiver requests can be justified on the basis of excess toxicity concerns related to age or unavailability of an age-appropriate formulation where the sponsor has demonstrated due diligence.

Proposed paediatric plan

Non-clinical studies

Juvenile toxicity studies

EMA position for PIP applications

The main purpose of juvenile animal studies is to identify potential safety concerns in view of the intended target indication. Juvenile studies should not delay paediatric trials but serve to improve the provisions to safeguard against intolerable harm and to monitor for age-specific risks, particularly in the youngest age group. With this in mind, when deciding on the need for a juvenile animal study (JAS), it is important to reflect clinically on the target population, e.g. in terms of its overall prognosis, but also on the ability to monitor any safety concerns (acknowledging the standard design aspects of paediatric oncology dose finding studies in the context of existing adult PK/PD and safety knowledge) or the option to stagger the development to generate safety and activity data in older children first. As mentioned in ICH S11, a JAS is designed to address safety concerns that cannot be adequately addressed in other nonclinical studies or paediatric clinical trials, including potential long-term safety effects.

The need for a juvenile animal study prior to initiation of a first paediatric study, usually conducted in a very selected patient population with dismal prognosis and clinically intensively monitored, might look different as compared to a target indication of front line therapy in a disease with high cure rates and e.g. the intent of novel therapies to reduce toxicities.

In that regard a reflection on the necessity of whether and by when juvenile animal data should be available to further safeguard development efforts, can be helpful, bearing in mind the objective of the PIP, which is to generate data sufficient to obtain a marketing authorisation.

When discussing the need for juvenile toxicity studies, include considerations on whether studies with one product inform same in class products. This could include the outcome of juvenile animal studies for products with the same target (when relevant, see for example https://www.ema.europa.eu/en/documents/scientific-guideline/results-juvenile-animal-studies-jas-impact-anti-cancer-medicine-development-use-children_en.pdf) or paediatric clinical data.

Additional nonclinical studies are more likely to be warranted:

- to specifically investigate concerns for effects on vital organs in patients below the age of 1-2 years with immature clearance pathways (incl. CYP, P-gp, renal excretion);
- prior to initiating studies in paediatric populations with good chances for long-term survival (prognosis to be reflected upon by the applicant);
- in case of target expression in the CNS and brain penetration;
- in case of potential concerns for toxicities that are difficult to monitor clinically (such as delayed CNS effects) or for which clinical data in adult populations are of limited relevance (e.g. long bone growth effects);
- for novel anti-cancer medicines targeting cell biology or developmental pathways with pleiotropic effects.

Additional nonclinical studies are less likely to be warranted:

- to characterise reproductive toxicities if similar concerns are known for pre- or combination treatments or when this is already a known class effect;
- if the potential concerns can be mitigated clinically e.g. bone marrow suppression, immune suppression; or in general, reversible toxicities for which biomarkers in clinical pathology allow early detection;
- to confirm effects that were identified as irreversible in adult animals;

- to support a study in children with limited life expectancy due to advanced / relapsed malignant disease with an IMP for which there are no significant concerns for vital organ functioning in the youngest target population.

Non-clinical pharmacology studies

Critically reflect on whether additional pharmacology studies in paediatric specific models are needed, e.g. as proof of concept (biomarker driven as necessary), ability to overcome resistance mechanisms.

Provide results of pre-clinical assessment of activity of a product in relevant paediatric-specific models both in vitro and in vivo as well as potential pre-clinical combinations.

FDA position for iPSP applications

Juvenile toxicity studies

Non-clinical testing of new drugs for toxicity in juvenile animals is not generally required as data on potential toxicity concerns that would inform monitoring strategies in proposed pediatric studies would be adequately provided by accumulated adult experience. For front-line therapies in diseases with a relatively good outcome, sufficient pediatric clinical data in the r/r setting would likely inform toxicity assessment plans in front-line studies. In select cases, if the mechanism of action predicts potential toxicity, evaluation in juvenile animals may be indicated.

Non-clinical pharmacology studies

Non-clinical pharmacology studies may inform initial dosing strategies for clinical investigation of those products where first in human experience is projected to occur in children.

Provide a rationale as to whether additional pharmacology studies in pediatric specific models are needed for purposes of demonstrating proof of concept, dosing considerations, and possible mechanisms of resistance and potential strategies to overcome resistance.

Provide results of pre-clinical assessment of activity of a product in relevant paediatric-specific models both in vitro and in vivo as well as potential pre-clinical combinations.

Quality development

EMA position for PIP applications

Discuss the appropriateness of the available formulation for the targeted paediatric population, taking into consideration disease and treatment specific implications.

Discuss and justify excipients in relation to age with a risk-based approach in relation to disease seriousness/severity and options for other treatments.

Suggest alternative strategies for administration when the proposed dosage form is not accepted. Include compatibility with common foods and drinks if appropriate. Include study of modification of the dosage form if necessary, with justification and safety of method of preparation.

Study compatibility with feeding tubes if likely to be used for drug administration.

Provide drug concentrations that allow suitable accuracy of drug measurement and administration with commonly available devices and/or apparatus or provision of such if not readily available.

Consider the safety of the persons preparing and/or administering the preparation and protection of the environment.

FDA position for iPSP applications

The quality development considerations as listed above for the EMA are in complete alignment with those of the FDA. Include complete details of the chemical composition of all active and inactive ingredients. Although dose and dosing recommendations for children may not be known early in a drug products design and development, early assessment of drug substance characteristics may be leveraged to identify potential dosage forms and formulations. Describe the appropriateness of the formulation across all pediatric age groups and include a description of the strategy/planning for development of pediatric -appropriate formulation that address the target pediatric population.

Paediatric clinical development:

EMA position for PIP applications

Discuss opportunities for inclusion of adolescents in adult studies to accelerate development in this age group, especially in situations where the clinical indication spans the adult and adolescent age group such as in Hodgkin lymphoma, some sarcomas, melanoma, including a discussion on disease similarity allowing to use extrapolation as supporting methodology.

The gold standard remains evidence generation as part of a randomised controlled trial (RCT). However, should there be reasons, e.g. lack of equipoise or feasibility making the conduct of an RCT not possible, justifications should be put forward discussing the basis for proposing other alternatives, such as single arm trials (SAT). In case a SAT is proposed, discuss and provide details how to generate comparative evidence. Any consideration for constructing external controls using patient level data, real world data (RWD) or Bayesian approaches using adult data as priors and/or the potential to utilising extrapolation should be discussed (reference is made to the EMA reflection paper on extrapolation - EMA/189724/2018). Justify your statistical assumptions. Outline approaches to constructing historical controls and propensity score matching and pre-specified statistical analysis plans (SAPs) to analyse differences between control and experimental arms.

Describe the safety issues most relevant to paediatric patients and what is in place to monitor and/or mitigate safety concerns identified, such as through independent data safety monitoring board.

Describe if input from relevant cooperative groups has been sought; ideally contextualised into the existing and future R&D landscape for the condition under discussion. Make reference to Paediatric Strategy Forum outcome conclusions as appropriate.

FDA position for iPSP applications

The required study to be included in the iPSP should be designed to provide sufficient information on dosing, toxicity and tolerability, and signal(s) of activity to both inform labelling and to inform further development of appropriate drug products as warranted by early, initial data within the context of clinical research strategies for specific diseases as supported by the clinical investigator community and in accordance with existing unmet clinical needs supported by patients, advocates, and clinicians. Sufficient details regarding the extent to which external input from competent clinical investigators and key opinion leaders has been sought in the clinical development planning should be included in the iPSP. Beyond the initial evaluation of a product in the pediatric investigation, contingent plans for more definitive development can be included including description of studies that might be conducted as part of a Written Request.

Timelines

Deferral:

EMA position for PIP applications

By default any paediatric development should start without delay.

Compare timelines of adult versus paediatric program and justify proposed timelines.

Justifications could include situations where there is the need to delay initiation of the first in child trial until availability of relevant adult data for safety reasons. Include reflections on any specific safety concerns and adult data needed to guide further decision making.

FDA position for iPSP applications

It is anticipated that pediatric studies described in the iPSP begin as soon as possible and before the submission of a NDA/BLA for the adult indication under development. Specific timelines are expected for submission of the protocol to FDA for review and approval, study activation and date of first subject enrolled, proposed study completion date, and date for submission of the final report. In certain situations, FDA will consider a plan for deferring conduct of pediatric studies until sufficient adult experience about safety and activity has been obtained. However, considerations on implementation of the planned pediatric studies and development should not be contingent upon timing of the original application. It is also understood that results of pediatric assessments may not be complete by the time a NDA or BLA for the investigational agent is to be submitted; planned requests for deferral of submission of study results should be included in the iPSP.