EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 February 2026
EMA/32831/2026
Non-clinical Working Party (NcWP)

Concept paper on the development of a reflection paper on proof-of-concept data to support the development of anti-cancer medicinal products in paediatric patients

Agreed by Non-clinical Working Party	5 February 2026
Adopted by PDCO	27 February 2026
Adopted by CHMP for release for consultation	16 February 2026
Start of public consultation	13 March 2026
End of consultation (deadline for comments)	30 June 2026

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Keywords	mechanism of action, paediatric oncology, non-clinical, weight of evidence, proof of concept

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1. Introduction

The availability of adequate proof-of-concept data (which may be a combination of non-clinical and clinical evidence) is a pre-requisite prior to the initiation of paediatric clinical trials. This data should consider the biological specificities of the target population in the context of the product's mechanism of action (1).

Driven by evolving global regulatory requirements, such as amendments (FDARA 2017) to the Pediatric Research Equity Act (PREA) in the United States (2), the European Medicines Agency (EMA) through its Paediatric Committee (PDCO) is observing an increasing number of paediatric investigation plans (PIPs) in oncology that are based on the product's mechanism of action rather than its targeted adult indication (3). Consequently, the Non-clinical Working Party is more frequently involved in the assessment of PIPs in which non-clinical proof-of-concept data is presented to justify the initiation of clinical development in paediatric oncology.

The emphasis of such assessments is on the adequacy of existing overall evidence and/or proposed non-clinical proof-of-concept studies to a) identify products for which non-clinical data may not reliably translate to the intended clinical setting, or non-clinical data indicate a potential lack of significant therapeutic benefit and to b) support feasible and appropriate development plans for products that have the potential to offer significant therapeutic benefit to the intended population while ensuring that safety considerations are not disregarded.

Given the absence of a structured regulatory framework for non-clinical proof-of-concept studies and the expressed interest from academic stakeholders in developing such a framework (4), the aim is to develop a reflection paper that outlines the elements considered important for guiding such assessments and associated development activities in paediatric oncology. The proposed weight of evidence approach is built on experience and methodology developed for the assessment of safety in paediatric drug development as described in the ICH S11 guideline (5) where the totality of evidence is routinely considered to guide the need for additional non-clinical studies.

2. Problem statement

Most paediatric cancers differ significantly from adult cancers in terms of their biological and clinical characteristics (6). Therefore, to support paediatric drug development of therapies initially developed for adult cancer indications, population-specific proof-of-concept data may be required. For example, in the case of a product developed for adult acute myeloid leukaemia (AML), the need for additional proof-of-concept data in paediatric AML should be considered, given the biological differences between adult and paediatric AML. A similar assessment would be needed for a product targeting ALK mutations in lung cancer, a malignancy that does not occur in children, but where the ALK-inhibition mechanism of action could be of relevance in paediatric malignancies such as neuroblastoma.

In addition, due to the low prevalence of paediatric cancers, the number of available patients for clinical trials is limited which increases reliance on robust non-clinical evidence to support development decisions. In the context of the Paediatric Regulation (7) which requires the submission of a paediatric development plan, it is essential to critically review the available evidence base in support of progression towards paediatric clinical trials. This evaluation is necessary to ensure targeted and feasible development strategies and to uphold the ethical imperative of protecting children through adequate non-clinical and clinical research (8). As a result, non-clinical pharmacology data specific to paediatric oncology may need to carry more weight within the totality of evidence to compensate for the inherent uncertainties and limited data typically available for development programmes targeting

paediatric-specific malignancies. This may relate, for example, to the overall sufficiency of proof-of-concept data to support paediatric development, the feasibility of development plans given the available constraints, and more specifically to supporting clinical trial design considerations, such as patient selection criteria (e.g., by identifying relevant tumour biology or biomarkers).

To address these challenges effectively, a structured and consensus-driven approach is needed to guide the assessment of proof-of-concept data supporting paediatric oncology drug development.

3. Discussion (on the problem statement)

The aim of the reflection paper is to provide recommendations that drive the generation and assessment of meaningful proof-of-concept data to support the development of medicinal products in paediatric oncology and to outline the challenges associated with evaluating such data.

A weight-of-evidence (WoE) based decision should be made to determine whether (and which) additional non-clinical investigations are warranted to support paediatric clinical development. This may be an iterative process, and as development progresses, adjustments to the plan may be required as new data become available. In this context, developing a comprehensive understanding of the available evidence with regard to the efficacy and safety of the product, the target disease, as well as the broader clinical context is essential. This informs the decision to either support a paediatric clinical development or grant a waiver of the obligation to develop (9). The reflection paper will discuss the following key evidence domains for the WoE assessment. This list is not exhaustive and does not imply any particular order of importance:

- Mechanism of action of the investigational medicinal product (and any combination partner) including the relevance of the target or pathway to disease biology
- Biology of the targeted malignancy (e.g. tumourigenic pathways, knowledge on biomarkers and their temporal evolution)
- Evidence from non-clinical disease models including their relevance and uncertainties in reflecting the intended clinical context, evidence of activity (e.g., effect size) and data on combination treatment schemes
- Use of other appropriate models for demonstration of primary pharmacology, including new approach methodologies (NAMs)
- Proof-of-concept data from same-in-class products (non-clinical or clinical)
- Pharmacokinetic considerations
- Clinical evidence with the drug in related conditions and other populations, where appropriate
- Safety considerations derived from non-clinical or clinical data (including age-specific risks) and contextualised safety data for combinations
- Clinical context, including disease prevalence and the feasibility of conducting a clinical study, the unmet medical need and the existing treatment options and ongoing developments in the target condition

Expert input and stakeholder involvement

Assessment of the data supporting the decision to enter clinical development is interdisciplinary. While clinical context is essential to contextualise non-clinical findings, responsibility for the non-clinical assessment and its conclusions lies with the non-clinical assessors. In addition to the involvement of non-clinical and clinical experts, the reflection paper will describe a proposed process for information exchange with stakeholders, including academic experts/academic consortia, industry and international

regulatory bodies such as the FDA. These stakeholders may contribute scientific input and expertise to inform the assessment of Paediatric Investigation Plans supporting anti-cancer drug development in children (although noted that regulatory decision-making remains the responsibility of the competent authorities).

4. Recommendation

The Non-clinical Working Party (NcWP) of the Committee for Human Medicinal Products (CHMP) recommends drafting a reflection paper on the non-clinical proof-of-concept data supporting the development of anti-cancer medicinal products in paediatric patients.

A reflection paper is considered the most appropriate form of guidance at this stage of knowledge and regulatory experience.

5. Proposed timetable

The concept paper will be published for a three-month public consultation period, to incorporate stakeholder feedback and ensure broad applicability. The Non-Clinical Working Party (NcWP) will consider all comments received during the public consultation when preparing the draft reflection paper. A workshop with external participants is planned in September 2026. The draft concept paper is planned for release for consultation in Q1 2026.

6. Resource requirements for preparation

The drafting of the reflection paper will involve representatives of the NcWP (including a Rapporteur) and other non-clinical and clinical experts from the EU network with expertise in the assessment of oncology medicinal products and non-clinical proof-of-concept data. It is anticipated that at least one plenary discussion at the NcWP will be needed.

7. Impact assessment (anticipated)

It is anticipated that the reflection paper will have an impact on the non-clinical evaluation of submitted PIPs in oncology, the development of paediatric medicinal products in oncology, and on the implementation of the New Pharmaceutical Regulation (10). The aim is to consolidate the current regulatory view on the assessment criteria for paediatric development programmes of medicinal products in oncology, and to facilitate consensus in the evaluation of such products by regulatory authorities.

8. Interested parties

Pharmaceutical industry, academia, European Union competent authorities, patients and health care professional groups. Consultation with other working parties [3Rs Working Party (3RsWP), Oncology Working Party (OncWP)], committees [(Committee for Human Medicinal Products (CHMP), PDCO and Committee for Orphan Medicinal Products (COMP)] and groups [Clinical Trials Coordination Group (CTCG)] will be initiated, where appropriate.

9. References to literature, guidelines, etc.

1. A.D. Pearson, R. Herold, R. Rousseau, et al. Implementation of mechanism of action biology-driven early drug development for children with cancer, Eur J Cancer, 62 (2016), pp. 124-131. https://doi.org/10.1016/j.ejca.2016.04.001

2. Oncology Center of Excellence Pediatric Oncology Program https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

3. Policy on the determination of the condition(s) for a paediatric investigation plan (PIP) / waiver (scope of the PIP / waiver) https://www.ema.europa.eu/en/documents/other/policy-determination-conditions-paediatric-investigation-plan-pip-waiver-scope-pip-waiver_en.pdf

4. Vassal G., Houghton P.J, Pfister S.M, Smith M. A., et al. International Consensus on Minimum Preclinical Testing Requirements for the Development of Innovative Therapies For Children and Adolescents with Cancer. *Mol Cancer Ther* 1 August 2021; 20 (8): 1462–1468. https://doi.org/10.1158/1535-7163.MCT-20-0394

5. ICH Harmonised guideline on nonclinical safety testing in support of development of paediatric pharmaceuticals https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-s11-nonclinical-safety-testing-support-development-paediatric-pharmaceuticals-step-5_en.pdf

6. Gröbner, S., Worst, B., Weischenfeldt, J. *et al.* The landscape of genomic alterations across childhood cancers. *Nature* **555**, 321–327 (2018). https://doi.org/10.1038/nature25480

7. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/

8. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use - https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R1901

9. D Karres, G Lesa, F Ligas, et al. European Regulatory Strategy for supporting childhood cancer therapy developments, Eur J Cancer, 177 (2022), pp. 25-29 https://doi.org/10.1016/j.ejca.2022.09.025

10. Reform of the EU pharmaceutical legislation - Public Health