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Advancing proof-of-concept data in paediatric oncology drug development

Workshop report

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1. Executive summary

EMA organised this workshop to receive a multi-stakeholder's perspective on the generation and use of adequate proof-of-concept data in paediatric oncology. This initiative is part of the EMA Non-clinical Domain workplan [1].

The aim of the workshop was to provide a platform for discussion to help inform the development of a future reflection paper on proof-of-concept data to support the development of anti-cancer medicinal products in paediatric patients.

The aims of the workshop were:

- to present the outcomes following the public consultation on the 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 [2];
- to gather stakeholders feedback on key questions, data needs, and perceived challenges towards collaborative implementation, enabling evidence-based paediatric oncology developments;
- to leverage learnings from oncology and discuss challenges in mechanism of action (MoA) based paediatric developments beyond oncology, and what is needed to support the implementation of MoA related provision in the new EU Pharmaceutical Legislation [3] across all therapeutic areas.

The workshop examined how proof-of-concept evidence should be generated, assessed, and applied, to support paediatric oncology drug development in an evolving mechanism-of-action–based regulatory environment. Participants were presented stakeholder feedback on a proposed weight-of-evidence (WoE) framework, explored scientific principles for evaluating non-clinical and clinical evidence, and discussed how to balance rigour, flexibility, feasibility, and patient needs in development decisions. The discussion brought together regulatory, industry, academic, clinical, and patient perspectives to identify key challenges and opportunities for improving evidence-based decision making. The meeting also considered how experience gained in paediatric oncology could inform future approaches in other therapeutic areas.

2. Public consultation feedback

Karen Van Malderen opened the meeting thanking everyone involved in drafting the Concept Paper and everyone who contributed with their comments during the consultation period. Maria Sheean presented the public-consultation feedback received between March and June 2026 on the published concept paper. Comments received will be assessed by the drafting group and used to inform the development of a future reflection paper.

Maria Sheean reported 11 submitted response documents containing 125 comments from industry, academic networks, patient advocacy, diagnostics, and individual contributors. Stakeholders generally endorsed a structured weight-of-evidence (WoE) framework but requested clearer definitions, scope, evidence thresholds, milestones, and decision routes. The challenge of balancing scientific rigour and proportionality, as well as predictability and flexibility of such a framework was highlighted.

The proposed WoE approach starts by assembling the totality of relevant evidence, then assessing each element for relevance and quality before integrating the weighted evidence into a multidisciplinary go/no-go decision on whether development can progress toward an early-phase paediatric clinical trial. The framework is also intended to guide whether additional evidence would be needed.

Evidence domains include disease biology, target and mechanism relevance, biomarkers, pharmacokinetics/pharmacodynamics, safety, model limitations, feasibility, same-in-class knowledge, clinical data in adults, combinations, and potentially real-world or off-label evidence. The list should remain adaptable and is not considered exhaustive because the relevant evidence depends on the product, disease, modality, treatment context, and evolving research questions.

Comments received during consultation highlighted both the need for predictable regulatory expectations and the importance of a flexible framework that can accommodate evolving evidence. EMA proposed early and iterative interaction between regulators, developers and academia, agreed milestones, transparent decision points, and context-specific evidence requirements rather than a rigid checklist to balance these needs.

It was clarified and agreed that the reflection paper will focus on scientific content and stakeholder engagement supporting non-clinical proof of concept in oncology. Detailed clinical-trial design, dose selection, formulation, broader safety guidance, clinical endpoints, access to a clinical trial, and implementation of the new pharmaceutical legislation are addressed or will be addressed through other guidance or processes. It was appreciated that nevertheless proof-of-concept evidence may inform clinical trial design considerations.

There was also agreement that operational expectations should be clarified where feasible. The proposed next step is to use the feedback to develop a detailed reflection paper and a framework to support decision-making.

3. Session 1: Stakeholders' views on the proposed weight of evidence framework and on the future process to support collaboration

3.1. Regulatory perspectives (EU and USA)

Dominik Karres framed the shared goal as timely access to safe, effective cancer therapies for children and adolescents. His presentation focussed on scientific principles—not regulatory procedures— as the basis for this workshop and the future reflection paper and described development as an iterative process: First defining the target product profile and key uncertainties and then generating evidence relevant to the next decision point. Proof-of-concept evidence is intended to support regulatory decisions on whether a product offers the prospect of significant therapeutic benefit and whether sufficient evidence exists to proceed to the next stage of development. Sufficiency is context-specific and depends on the product, the intended target population and existing unmet needs.

Non-clinical proof-of-concept evidence is not intended to predict clinical success or directly support patient-care decisions. Rather, the combined evidence should enable informed decision-making on the way forward.

Use cases involving HER2 antibody-drug conjugates and PARP inhibitors [4, 5] illustrated this context-specific approach, demonstrating how paediatric-specific evidence, biological rationale, and feasibility considerations influence development decisions. The key conclusion was that evolving, product-specific evidence anchored in patient relevance should drive go/no-go decisions rather than broad class assumptions. It was also highlighted that the PIP framework allows development plans to be refined as science and evidence evolve, and priorities to be adjusted as appropriate, to support focused, feasible and timely paediatric drug development.

The scientific principles underpinning decision-making emphasised that any need for additional proof-of-concept data should always be assessed against the evolving research question and target product profile.

Given that regulatory decisions related to proof of concept reflect the evidence and stakeholder input available at a given time, sharing case-specific decisions and lessons learnt remains key to advancing science for the benefit of the broader community.

During the panel discussion, Martha Donoghue outlined how FDA practice already incorporates an integrated assessment of biological rationale, clinical data, non-clinical evidence, and mechanism-of-action considerations when determining paediatric development needs. She highlighted broad alignment with the principles being discussed and welcomed continued collaboration.

3.2. Industry perspectives

In her presentation, Gesine Bejeuhr highlighted industry support for mechanism-of-action–based paediatric development while calling for clearer evidence thresholds, decision trees, practical examples, and alignment with existing guidance. She advocated a scientific roadmap to improve regulatory predictability without imposing uniform requirements. Gesine Bejeuhr also emphasised the importance of coordinatiing European and U.S. paediatric development requirements to avoid fragmented trials, duplicated studies, and delays in patient access identifying continued regulatory communication and harmonisation were identified as priorities.

In his presentation, George Kirk outlined the paediatric strategy for a folate receptor (FRα)–targeting antibody-drug conjugate, drawing on existing biological evidence. This included a review of existing target evidence, planning for non-clinical testing in osteosarcoma and ependymoma models, and the development of a clinical study design in parallel. The non-clinical work would inform whether and in which paediatric tumour types to proceed taking into account target-expression levels and the limited availability of relevant models. Clinical planning was therefore progressing in parallel with non-clinical evidence generation, while initiation of clinical studies would depend on sufficient paediatric proof-of concept evidence.

During the panel discussion, George Kirk explained that confidentiality agreements, including master agreements with institutions, can enable companies to share commercially sensitive information. Pamela Kearns added that academic organisations should use confidentiality agreements and declarations-of-interest policies to provide companies with clarity on how confidential information such as expert input is protected and potential conflicts of interest are managed.

When asked how to balance predictability and flexibility within the WoE framework, Gesine Bejeuhr suggested defining key evidence domains and decision principles supported by practical guidance and case examples which she considered essential for implementing the new MoA PIP requirements. She also highlighted the importance of maintaining flexibility for voluntary paediatric research that may be conducted outside the scope of these requirements.

3.3. Academic translational perspectives

Jan Molenaar described the work of ITCC (Innovative Therapies for Children and Adolescents with Cancer) to define a minimum non-clinical proof-of-concept framework, subsequently applied in systematic target reviews and prioritisation workshops across 12 paediatric cancer types. He explained that stronger non-clinical evidence could help address the limited translation of new therapies into paediatric care, given children's distinct tumour biology and small patient populations [6-8].

The framework assesses target and compound evidence, including target presence and validation, toxicity, biomarkers, resistance, and combinations, in terms of data quality and strength of effect. Jan Molenaar cautioned that testing only in a favourable model, treating statistical significance as evidence of meaningful activity, using clinically unrealistic drug exposures, or evaluating single agents when combinations are intended can weaken conclusions.

He noted that shared data and model resources are expanding, including a portal and a repository of more than 350 paediatric patient-derived xenograft models, although suitable models remain limited for some tumour subtypes and modalities. He also raised questions about whether negative proof-of-concept evidence could support a waiver and whether a paediatric non-clinical plan should form part of a PIP. These questions were considered in the context of the PARP inhibitor and HER2-targeting antibody-drug conjugate cases presented by Dominik Karres [4,5], which illustrated how product-specific evidence can inform paediatric development decisions and how PIPs can be refined as evidence evolves.

During the discussion, Malcolm Smith emphasised that paediatric oncology agents should be prioritised according to their potential to produce robust tumour regressions or leukaemia remissions at meaningful rates. As drug development has shifted toward biomarker-defined populations, broad non-clinical efficacy testing may add less value when adult clinical evidence and paediatric tumour biology already identify a plausible responsive population. He argued that additional testing should therefore address a clearly defined, decision-relevant uncertainty, while accounting for the ethical, resource, and time costs of delaying clinical evaluation in children.

For combination therapies, Malcolm Smith recommended beginning with evidence of meaningful single-agent activity rather than relying primarily on non-clinical synergy. Experience from adult oncology and the foundations of curative paediatric combination chemotherapy suggest that combining independently active agents provides a stronger basis for success. He cautioned, that apparent synergy may also amplify toxicity in normal tissues and require dose reductions that undermine effective exposure. Thus, synergy alone should meet a particularly high evidentiary bar when used to justify paediatric evaluation of an otherwise insufficiently active agent [9,10].

When asked about investigator-initiated trials sponsored by academia, and the level of engagement that could realistically be expected from industry, Malcolm Smith supported collaboration between industry and academic trial groups so that investigator-led trial data could inform further clinical development.

In the discussion of the current experience with new approach methodologies (NAMs), Jan Molenaar highlighted their potential to represent a broader range of patients and support the study of some immunological interventions, while noting that their ability to predict clinical outcomes remains uncertain.

3.4. Academic clinical research perspectives

Pam Kearns emphasised that proof-of-concept evidence should support a practical decision: whether a therapy merits evaluation in children. She advocated a scientifically robust and proportionate approach, adaptable to different treatment types, and cautioned against additional non-clinical work that delays clinical evaluation without resolving a meaningful uncertainty.

She emphasised that evidence needs depend on the disease, patient (sub)group, unmet need, and intended use of the medicine. Adult data may be informative where disease biology is shared, but should not replace paediatric-specific evidence when it adds value; potential acute and long-term toxicity should also inform decisions.

Pam Kearns highlighted the importance of studying combinations when this reflects how a therapy is expected to be used, rather than requiring single-agent trials when the evidence suggests that the medicine will not be sufficiently effective alone. She also called for meaningful opportunities for clinical academic and patient advocate consortia to contribute their perspectives on disease severity, existing treatments, safety, feasibility, and patient needs.

During the panel discussion, Elizabeth Fox emphasised that evidence generation should answer practical clinical questions, demonstrate meaningful activity, and include assessment of safety, pharmacology, biomarkers, resistance mechanisms, and target relevance. She highlighted the importance of evidence thresholds that reflect biological uncertainty, unmet need, and clinical context.

3.5. Patient perspectives

Patient representatives were invited to provide their perspectives during the panel discussion. Valentina Jalby, a young patient expert, explained that patients need clear communication about trial goals, scientific rationale, risks, support structures, and outcomes throughout the study journey. She stressed that understanding the science and maintaining transparent communication improve trust and participation.

Delphine Heenen provided a recorded statement in which she emphasised that no paediatric trial should proceed without strong non-clinical evidence supporting a realistic possibility of benefit and highlighted the importance of carefully designed eligibility criteria. She advocated for maximising both scientific validity and patient value when selecting clinical studies.

4. Session 2: Going beyond oncology – learnings and next steps

4.1. Mechanism of action under the new legislation

Izabela Taborska reviewed the relevant provisions of the upcoming European pharmaceutical legislation, expected to be formally adopted in late 2026, and explained how mechanism-of-action considerations will influence paediatric waiver assessments and stepwise paediatric development plans.

She identified the responsibility of the industry to present existing data in applications, and that of EMA to be able to assess such data. She also acknowledged that implementation of the new legislation may create an opportunity for the academic community to engage as well, referring to the mechanism of action in waivers. She also explained that new guidelines will be developed by EMA, in consultation with the Commission, the competent authorities of the Member States and relevant interested parties, to provide greater predictability in the application of the legislation.

4.2. Vision and education

Ricardo Fernandes explained the challenge of connecting the broader paediatric research ecosystem so that it can identify therapeutic needs, interrogate disease and target science, generate missing evidence across the lifecycle, and support development where justified. He emphasised that oncology provides an advanced example but should not be treated as a universal template.

Approaches, tools, and lessons from oncology should be tested against the maturity, specificity, and evidence base of each non-oncology therapeutic area. Ricardo Fernandes recommended realistic, stepwise adaptation rather than overfitting oncology solutions, with requirements and procedures considered in parallel.

Ricardo identified priorities including education and agreement on terminology, fit-for-purpose capacity building, multi-stakeholder engagement, mapping of knowledge and infrastructure gaps, accessible data and expertise, sustainable funding, and clear boundaries between pre-competitive and competitive work.

The next steps identified were to refine existing frameworks, engage existing forums such as Enpr-EMA, identify resource needs, select sufficiently mature therapeutic areas, test transferable elements, and develop case studies and worked examples. Expectations should be managed, as implementation will require iterative learning over time.

4.3. Scientific content and decision making

Sabine Scherer reported that non-oncology preparations for proof-of-concept data assessment are less advanced and that case studies, including on Alzheimer's disease, indicated potential value in mechanism-of-action-based PIPs despite limited published data. Several conditions on the class-waiver list may need to be reviewed, with case-by-case assessment of medical need, all available evidence, off-label and same-class data, and feasibility where adult extrapolation is limited.

It was noted that paediatric programmes should be based on robust science and should include futility stopping criteria so that a non-clinical programme does not automatically proceed to a clinical study. A modified stepwise PIP could be useful where clinical progression is not necessarily expected, supported by early interaction and structured pre-competitive therapeutic-area discussions. The need for robust scientific foundations, feasibility assessments, early dialogue, and stepwise development strategies before requesting paediatric studies was emphasised.

4.4. Discussion

During a short panel discussion concluding this session, Ricardo Fernandes said that the EnprEMA community should map existing research and gaps, support new research, and bring stakeholders together. He described EnprEMA's potential contributions as providing education, helping to shape initiatives, and mobilising communities.

Asked about potential avenues to support the academic community's engagement, Izabela Taborska noted possible EU funding routes, including programmes for rare and very rare cancers and the Horizon Europe partnership on rare diseases. She said that there was no specific paediatric initiative at the time but acknowledged that the community could seek EU funds, if available, to support development opportunities.

Sabine Scherer commented on the translatability of principles across rare and non-rare diseases, and across oncology and non-oncology. She noted that proof-of-concept principles should retain scientific rigour, but that feasibility, needs, and treatment goals may vary depending on the context. She emphasised the need for case-by-case assessment and said that stepwise approaches could be valuable.

5. Closing Remarks

Karen Van Malderen closed the workshop by confirming that the presentations and a workshop report will be shared, while the drafting group will use the discussion to develop the reflection paper and, in this context, a further public consultation.

The drafting group will use the consultation feedback, workshop comments, questions, and stakeholder perspectives to develop a reflection paper on proof-of-concept evidence in paediatric oncology. The

paper is expected to address operational criteria, evidence domains, model uncertainty, stakeholder engagement, patient voice, combinations, and illustrative case studies.

Regarding mechanism of action under the new pharmaceutical legislation, EMA is expected to develop general guidance explaining the scientific application of the new mechanism-of-action waiver provisions.

6. List of speakers and panellists

Karen Van Malderen is a non-clinical assessor at the Belgian Federal Agency for Medicines and Health Products and is a member of the Paediatric Committee and the NcWP (recently elected as chair) at EMA. She is also a member of the drafting group that developed the concept paper.

Maria Sheean is a scientific officer in the Paediatric Medicines Office at EMA. She provides scientific support to the NcWP and has also been part of the drafting group that developed the concept paper.

Dominik Karres is a scientific officer in the Paediatric Medicines Office at EMA. He is also a member of the drafting group that developed the concept paper.

Gesine Bejeuhr is global paediatric leader at Bayer, advising global paediatric development teams and is responsible for paediatric regulatory policy, with 20 years of experience, including the organisation of two mechanism-of-action PIP workshops for the EFGCP's Children's Medicines Working Group. At the workshop she presented an industry view on behalf of EFPIA.

George Kirk is a global franchise head in Late Oncology at AstraZeneca and is also the lead of the AstraZeneca Paediatric Oncology Development Team (PODT) which is accountable for developing and delivering paediatric strategies across the oncology portfolio. At the workshop, he presented an industry view.

Jan Molenaar is a professor at the Princess Maxima Centre at Utrecht University. He is a research scientist specialised in target identification and validation in paediatric solid tumours. He is the head of the paediatric cancer precision medicine programme at the Princess Maxima Centre in Utrecht.

Pam Kearns is emeritus professor of Paediatric Oncology at the University of Birmingham, where she was director of UK's national childhood cancer clinical trials unit for 13 years and she is now president of the European early phase trials consortium; ITCC: Innovative Therapies for Children and Adolescents with Cancer, and a member of the EnprEMA coordinating group on behalf of ITCC.

Martha Donoghue is a paediatric haematologist/oncologist by training and serves as the associate director of Paediatric Oncology and Rare Cancers in the Oncology Center of Excellence at the U.S. FDA.

Malcolm Smith is a paediatric oncologist who works in the NCI Cancer Therapy Evaluation Program. He has led NCI consortia for paediatric non-clinical testing over the past 20 years and works closely with the NCI-supported clinical trials programmes for children with cancer, including the Paediatric Early Phase Clinical Trials Network and the Children's Oncology Group.

Elizabeth Fox is a paediatric oncologist with 30 years of experience in early-phase clinical trials for children with cancer. She is the senior vice president for Clinical Research Administration at St Jude Children's Research Hospital and currently serves as the chair of the Paediatric Early Phase Clinical Trial Network.

Valentina Jalby is a patient expert representing the youth patient community. She is 13 years old and is a member of the TEDDY Kids Network, the Patient Expert Group for the INVENTS Project and the Patient Advisory Board for the GAPP study.

Delphine Heenen is the managing director and co-founder of the Belgian foundation KickCancer and a member of Childhood Cancer International. She is the (step)mother of four boys, one of whom was diagnosed with cancer at the age of 9. The lack of innovative treatments offered to him drove her and her family to found KickCancer.

Izabela Taborska is a legal and policy officer working at the European Commission in DG SANTE, unit D1, which deals with policy, authorisation and monitoring of medicines for human use. She has been working at the European Commission since 2011 and currently works on paediatric medicines files.

Ricardo Fernandes is the chief medical officer for conect4children, a pan-European network supporting paediatric medicines development and paediatric trials. He is also the lead of the STAND4Kids Portuguese paediatric trial network, an associate professor in clinical pharmacology at the University of Lisbon, and a consultant paediatrician. He is currently the elected co-chair of EnprEMA.

Sabine Scherer is a paediatrician by training and an assessor at the German Federal Institute for Drugs and Medical Devices – BfArM. She currently serves as the chair of the EMA Paediatric Committee (PDCO).

7. Abbreviations

MoA – mechanism of action

WoE - weight-of-evidence

NAM – new approach methodology

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