CBG MEB | COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

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Extrapolation as basis for paediatric marketing application

A review of paediatric investigation plan, summary of product characteristics and European public assessment reports covering the full spectrum of paediatric marketing application

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Table of content

Abstract: **2**

Introduction **3**

Challenges in paediatric drug development *3*

Paediatric regulation *3*

Paediatric extrapolation *4*

Key assumptions for paediatric extrapolation *5*

Modelling and simulation *6*

Study objective *6*

Materials and methods **7**

PIPs suitable for inclusion *7*

Extracted information from PIPs *7*

Extracted information from SmPC's *7*

Extracted information from the EPAR *8*

Analysis *8*

Results **9**

PIPs eligible for inclusion *9*

Extracted information from PIPs *9*

Key findings in KBEs 9

Study distribution in KBEs 10

Extracted information from SmPC's *13*

Indications in KBEs 13

Approved indications of KBEs 13

Extracted information from the EPAR *15*

Indications in procedures 15

Role of extrapolation 16

Discussion **18**

PIPs eligible for inclusion: *18*

Extracted information from PIPs: *18*

Extracted information from SmPCs: *19*

Extracted information from EPARs: *19*

Limitations *20*

Conclusions **21**

Bibliography **22**

Supplemental information: **23**

Abstract:

Introduction:
To promote the use of authorized medical products for paediatrics, the Paediatric Regulation was implemented in the EU in 2007, requiring pharmaceutical companies to submit a paediatric investigation plan (PIP) to ensure appropriate data is gathered in the paediatric population to determine the benefit/risk balance. Modelling and simulation analyses are becoming increasingly more important in PIPs to provide valuable insights. However, it currently unclear whether the planned age range in compliant PIPs has also been approved. In addition, it is unclear whether there are differences between the regulatory route (full, partial or no extrapolation) taken and the overall approved age range. This study aims to provide a comprehensive overview on the use of extrapolation in compliant PIPs and identify the types and frequency of extrapolation in marketing applications for paediatric indications, and examine their impact on regulatory decision-making processes.

Methods:
To extract data for all medical products approved by the European Medicines Agency, publicly available PIPs registered from 2007 to 2022 were extracted and filtered to only include compliant PIPs. Information was collected on the planned indication, types of studies conducted, and planned age range of the paediatric population involved. Subsequently, extracted information on age range approved in the indication and, if applicable, additional weight requirement from the Summary of Product Characteristics (SmPCs). Finally, information of the conducted paediatric studies was extracted from the European Public Assessment Report (EPAR).

Results:
Since the introduction of the paediatric regulation in 2007, 264 (10.1%) of the PIPs have been compliant. In the 264 compliant PIPs, 286 unique KBEs were extracted, of which 48 (16.8%) specified one or more extrapolation studies. Extrapolation studies were conducted to evaluate efficacy, pharmacokinetics (PK), pharmacokinetics/pharmacodynamics (PK/PD), and dose-finding. Interestingly, 35.6% of the indications applied extrapolation during marketing authorisation application, which is almost double the defined percentage in the KBEs. Marketing application procedures that used an extrapolation approach, lead to a reduction of 1.4 years in the average minimum approved age compared to procedures that did not use extrapolation. When extrapolation is not utilized, there is a difference of 3.2 years between the average minimum age specified in the PIP and the average minimum age approved in the SmPC. However, with extrapolation, both averages align at 3.8 years.

Discussion:
The role of paediatric extrapolation appears to be limited in publicly available paediatric investigation plans. However, from the marketing application procedures, it is apparent that paediatric extrapolation has a more pronounced role in the approval of paediatric indications. Interestingly, procedures that used extrapolation have a lower approved minimum age compared to procedures that did not use extrapolation. In addition, paediatric extrapolation procedures resulted, on average, in the same approved age range as planned in the paediatric investigation plans. These findings imply that the use of paediatric extrapolation could translate in broader approved paediatric age range and could therefore reduce off-label use.

Key words: paediatric investigation plan (PIP), extrapolation, European Medicines Agency (EMA), efficacy, marketing authorization, regulatory decision making.

Introduction

Challenges in paediatric drug development

Despite the importance of providing safe and effective treatments for paediatrics, many drugs are still prescribed off-label and without sufficient evidence of their benefit/risk balance. Up to 50% of all prescribed drugs in five hospitals in United Kingdom, Sweden, Germany and the Netherlands were prescribed off-label or unlicensed.[1] As a consequence, paediatrics have become 'therapeutic orphans' due to incomplete information about dosage, safety and efficacy of medicines due to challenges in conducting clinical trials involving paediatrics.[2] Conducting clinical trials in paediatrics presents ethical and practical challenges, including difficulties around obtaining informed consent and data collection. For example, efforts are made to minimize the volume of collected blood during paediatric studies.[3] Adequate justification for blood volumes used should be included in study protocols. Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs) assess these justifications thoroughly and have the authority to determine the maximum permitted blood volume collected for research purposes.

Besides ethical and practical challenges, the unique pharmacokinetic and pharmacodynamic properties in paediatrics pose difficulties in determining appropriate drug dosing and administration.[4] Factors such as absorption, distribution, metabolism and excretion (ADME) influence drug concentrations over time. ADME processes can differ between adults and paediatric populations, affecting the drug's pharmacokinetic profile and optimal dose. Moreover, ADME processes may vary within different age groups of paediatric patients, which could indicate that multiple dose adjustments over the paediatric age range are required.[4]

Due to the differences in physiology, metabolism, and dosage requirements, formulations suitable for adults may not always be appropriate for paediatric patients. The lack of age-appropriate formulations limits clinical studies in paediatrics. Therefore, there is a critical need for age-appropriate formulations in paediatrics, that enable accurate dosing and enhance patient compliance. Various formulations such as liquids, suspensions, and chewable tablets may be necessary for different age groups of paediatric patients. Different drug concentrations within these formulations may be required as well.[3] However, developing age-appropriate formulations for paediatrics faces challenges, including high research and development costs and a smaller patient population, leading to low return on investment.[5] Despite these challenges, there are currently multiple initiatives aimed at developing age-appropriate formulations for paediatric populations.[4]

Paediatric regulation

To address the issue of inadequate access to safe and effective medical products for paediatrics in the European Union (EU), the Paediatric Regulation was implemented on January 26th, 2007.[6] The primary goal of the regulation was to promote the utilization of authorized medical products in paediatric patients while minimizing the use of off-label drugs. This regulation aimed to ensure that paediatrics have the same access as adults to high-quality medical products that have undergone ethical research and appropriate authorization.

The Paediatric Regulation requires new medical products to be investigated in paediatrics from birth to 18 years of age who have a therapeutic need. Therapeutic need identifies specified medicinal conditions or diseases in the paediatric population that require treatment, considering factors including prevalence and severity of conditions, availability, and suitability of alternative treatments, including efficacy, profile of side effects and any potential paediatric safety issues, along with relevant data from studies conducted in other countries. The assessment of these factors helps establish the inventory of therapeutic needs.[7] To achieve compliance with the paediatric regulation, pharmaceutical companies are required the submission of a prospective paediatric investigation plan (PIP) to the

Paediatric Committee (PDCO) of the European Medicines Agency (EMA) for assessment.[8] A PIP is a strategic plan developed to guarantee that appropriate data is collected to support the assessment of the benefit-risk balance and the authorisation of a medicinal product for paediatric use.

PIP submission must occur no later than the completion of adult pharmacokinetic (PK) studies.[7] Requests for waivers of paediatric development are permitted but must be supported by appropriate justifications. A waiver entails the exemption from providing the required information for specific medicinal products or classes of medicinal products. This exemption is granted if there is evidence indicating the specific medical product is likely to be ineffective or unsafe for some or all of the paediatric population, the disease or condition for which the specific medicinal product is intended occurs only in adult populations, or the medicinal product does not offer a significant therapeutic benefit compared to existing treatments for paediatric patients. Additionally, it is possible to request a deferral for the initiation or completion of specific actions outlined in the PIP. This deferral must be supported by scientific, technical, or public health-related justifications. For example, it is deemed appropriate to prioritize conducting studies in adults before initiating paediatric studies. [7]

Paediatric extrapolation

Before initiation of paediatric studies, a substantial body of knowledge is often already obtained in adult populations. Neglecting to integrate this information into paediatric drug development would represent a missed opportunity to enhance the efficiency and safety of the drug development process. Integration of adult information in paediatric drug-development can be achieved through paediatric extrapolation, which involves extending knowledge from studies conducted in specific patient groups to make inferences on the applied for paediatric population.

Paediatric extrapolation is defined by the EMA in the reflection paper as: “extending information and conclusions available from studies in one or more subgroups of the patient population (source population(s)), or in related conditions or with related medicinal products, in order to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the amount of, or general need for, additional evidence generation (types of studies, design modifications, number of patients required) needed to reach conclusions”.[5]
The more recent International Council for Harmonisation (ICH) E11 draft Guideline defines paediatric extrapolation as “an approach to providing evidence in support of effective and safe use of drugs in the paediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the paediatric (target) and reference (adult or other paediatric) population.”[9] While the EMA defines paediatric extrapolation with the aim of reducing the number of clinical studies in paediatrics, the ICH defines paediatric extrapolation with the aim of providing evidence in support of effective and safe use of drugs in the paediatric population.

Paediatric extrapolation can be categorized into three subgroups: full, partial and no extrapolation (Figure 1). Full extrapolation allows for the direct application of efficacy data obtained from studies conducted in the reference population, i.e. adults or other paediatric populations, to the intended paediatric target population. In the case of partial extrapolation, efficacy data are partially extrapolated and supported by specific efficacy studies conducted in the target paediatric population. When no extrapolation is used, efficacy and/or safety studies are exclusively conducted in the paediatric target population to gather the necessary data for assessing the benefit-risk profile.

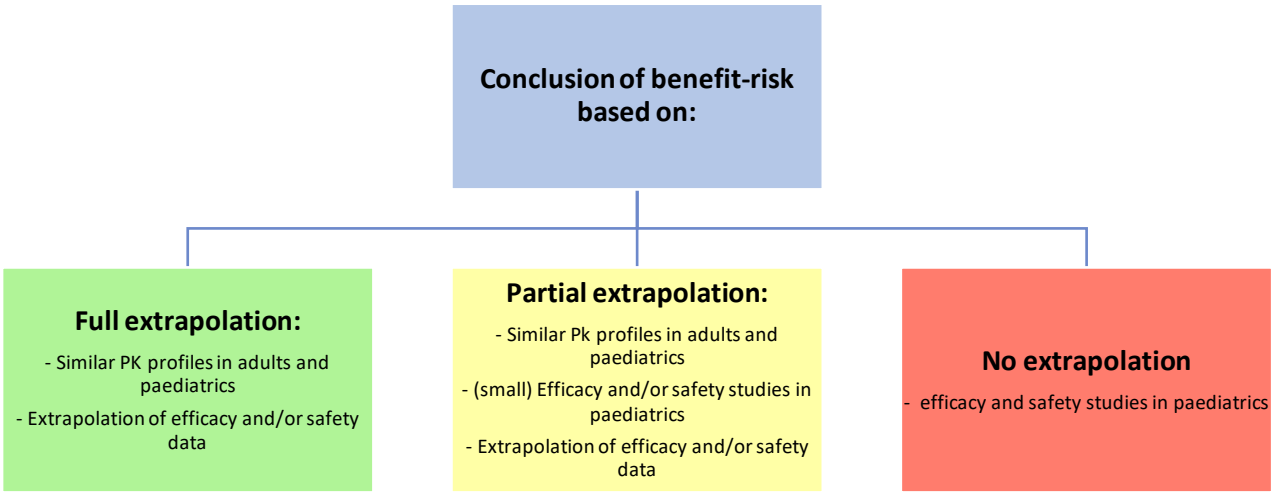

Figure 1. Classification of Benefit-Risk conclusion based on full, partial or no extrapolation.

Key assumptions for paediatric extrapolation

Paediatric extrapolation relies on several key assumptions to derive expectations for drug effects in the target population. These assumptions can be categorized into three main assumptions: disease manifestation and progression, pharmacology and clinical response to treatment.[6]

Disease similarity indicates that the pathophysiology, manifestation, and progression of the disease in the source or reference population are similar to the target population. The characterization of the similarities and differences between the two populations should be clearly defined by assessing the influence of potential physiological and maturation-related factors. By comprehending the differences between populations, it will enable predicting the disease course in the target population.

Pharmacology similarity assumes that the drug exposure profiles (PK) and response to drugs in the source and target populations are similar. It requires characterization of similarities and differences between two populations based on the influence of potentially significant factors (such as body size and body mass index) based on physiological and maturation-related differences in absorption, distribution, metabolism and excretion (ADME), PD effects, and toxicity.

Clinical response similarity assumes that the efficacy and safety in the source and target populations are similar. To measure the similarities and extent of variations in clinical response across populations, physiological and maturation-related differences are considered. The balance of benefits and risks within relevant subgroups of the target population should be described and, if possible, predicted by quantitative synthesis or meta-analysis of existing treatment data.

The type of extrapolation applied depends on the level of uncertainty associated with the three primary assumptions (Figure 2). Lower uncertainty in these assumptions reduces the need for extensive data generation in efficacy studies.

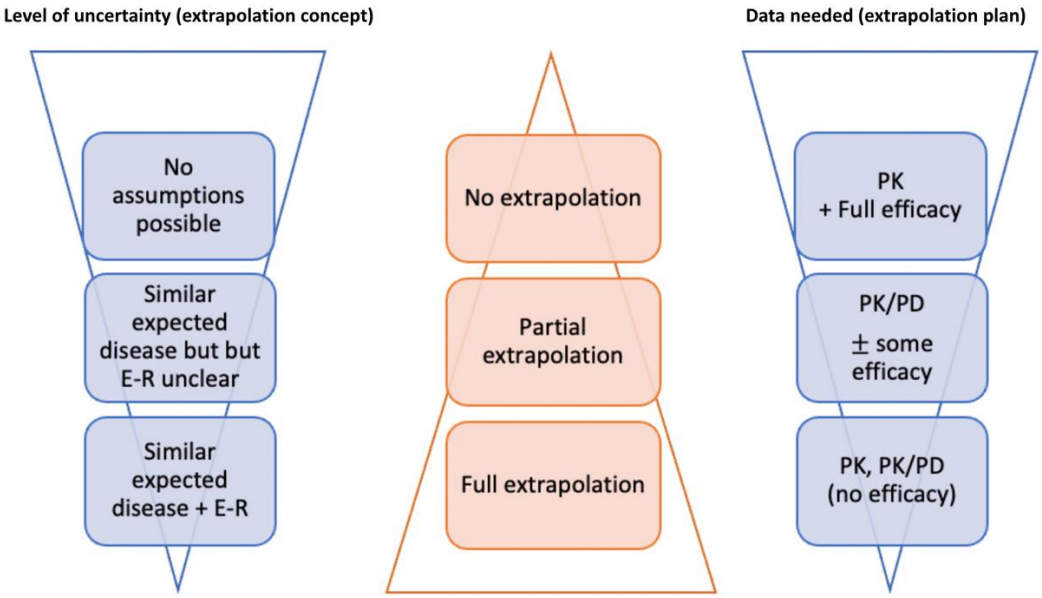

Figure 2. relationship between degree of uncertainty in assumptions, type of extrapolation and data needed in types of studies in PIPs.

Modelling and simulation

Modelling and simulation is a valuable approach to gain insight into complicated systems or processes by using mathematical models, and to apply these models to simulate real-world scenarios.[10] In terms of paediatric extrapolation, M&S can be applied to study the time course of drug exposure and response, enabling the prediction of parameters such as clearance and volume of distribution. There are several types of M&S techniques that can be utilized in pharmacometrics, such as population pharmacokinetic (pop-PK) models, physiologically-based pharmacokinetic (PBPK) models and disease progression models. PK models describe the concentration of a drug in the body over time, while PKPD models incorporate the relationship between drug concentration and pharmacological response. Pop-PK modelling is a valuable tool for gaining insight into the variability of drug response in different populations and makes it possible to extend information from adult indications to paediatric indications. Disease progression models aim to describe the natural history of a disease, while meta-models combine information from multiple sources to improve the accuracy of model predictions. Overall, the application of modelling and simulation can provide valuable insights into drug development and application in different populations, including paediatric patients.[10]

Study objective

Since the implementation of the Paediatric Regulation, paediatric drug development in the EU can be expected to be more structured and efficient as regulatory authorities provide early comments on the appropriateness of the paediatric development program for marketing application in the paediatric population. Publication of the EMA reflection paper and draft ICH Guideline on paediatric extrapolation aimed to further enhance paediatric drug development by promoting the role of paediatric extrapolation. It is however unclear what the exact role of paediatric extrapolation in marketing application for paediatric indications is. This study aims to provide a comprehensive overview of the use of extrapolation in paediatric drug development and its role in improving regulatory decision-making. Specifically, this study will analyse the use of extrapolation in compliant PIPs and identify the types and frequency of extrapolation studies used in marketing applications for paediatric indications submitted to the EMA. Additionally, it will examine the impact of these extrapolation studies on the regulatory decision-making processes.

Materials and methods

PIPs suitable for inclusion

A Paediatric Investigation Plan (PIP) is a regulatory document required by the European Medicines Agency for the development and authorization of medical products for use in paediatrics. It provides an overview of the required studies that are necessary for establishment of the benefit-risk balance and, ultimately, the approval of a paediatric indication for a medical product. To investigate the role of paediatric extrapolation in PIPs, the first step was to extract data for all published PIP decisions by the European Medicine Agency (EMA). Publicly available PIP decisions registered from 2007 to 2022 were extracted using the EMA website (https://www.ema.europa.eu/en/medicines/download-medicine-data). This file includes information regarding the active substance name, therapeutic area, URL corresponding to the PIP document and compliance procedure number.

This study aimed to distinguish and include PIP decisions that had received agreement on an investigation plan that specified to-be-performed studies. A selection function was therefore applied to the "decision type" column to specifically target P (decision agreeing on investigation plan, with or without partial waiver(s) and/or deferral(s)) and PM (decision on the application for modification of an agreed PIP). Additionally, this study focuses exclusively on compliant PIPs due to their inherent fixed nature of data. Since compliant PIPs are finished, they provide a clear and concise overview of regulatory requirements of the Paediatric Regulation. To select only compliant PIPs, a filter function was applied in Excel by unchecking the "no" option in the "compliance check" column.

Extracted information from PIPs

All decision files of compliant PIPs were downloaded. PIPs without a published decision file on the EMA website were excluded from the study and labelled as "missing". If two PIPs were found to be duplicates, but listed under different brand names, only one of them was included in the analysis. In cases where the PIP document contained multiple key binding elements (KBE) sections (for different indications), each of the KBE was treated as an unique KBE table. An example of this can be seen in the PIP decision for Tenofovir Disoproxil Fumarate (Truvada) (EMA/731471/2015), where two sections titled 'measures' were included, resulting in two unique KBE tables.

For each unique KBE, information was collected on waiver(s), indication(s) and paediatric population involved, including the indicated minimum and maximum age of the paediatrics. In this study, if no age range is specified, but terms such as "adolescents" are used, the corresponding age category according to ICH guidelines[9] (Table S1) was imputed. The term "preterm new-born infants" is assigned as zero years of age. Additionally, the terms "age of menarche" and "pubertal boys" were both assigned as 12 years of age.[11-12] The types of studies conducted (quality, non-clinical, clinical and extrapolation) were recorded, as well as whether efficacy studies were conducted in the clinical trials. These studies were subsequently categorised based on study aims. Besides, data was collected on the minimum and maximum age in the clinical and extrapolation studies. It was also noted whether an age-appropriate formulation was developed in the PIP. If a quality study indicated that a new product would be developed, it was considered an age-appropriate formulation.

Extracted information from SmPC's

Information in the Summary of Product Characteristics (SmPC) was extracted via the EMA website for the indication(s) that matched the PIP. If no EPAR was available for the medicinal product related to the PIP, the SmPC was documented as "missing". The absence of an EPAR may be due to recent medication approval and corresponding ongoing publication process by the EMA, or a decentralised or national marketing application approach. Information about the minimum and maximum age range included in the indication for the medical product was extracted by screening section 4.1 of the SmPC available on the EMA website for the corresponding indication. If section 4.1 did not provide age-

related information, it was assumed that the medical product was authorized for use in individuals aged 0 to 18 years. The indicated ages submitted in the PIPs were assessed to determine whether the indications were approved according to the SmPC. The indications were categorized as fully approved, partially approved, or not approved. Medicines that had lost their authorization were labelled as “no longer authorized”, while medicines without SmPC were excluded and labelled as “missing”.

Extracted information from the EPAR

The information on the studies conducted was obtained by screening the document titled “Procedural Steps Taken and Scientific Information After Authorization”. This document was screened for procedures related to the extension of indication to paediatrics. The scope and procedure number of the study were documented. Besides, the initial marketing-authorization document was also screened to determine whether a request for a paediatric indication was already included at time of initial marketing application, usually for the adult indication. Next, the report corresponding to the procedure number was accessed to extract information regarding the extrapolation approach. If the report corresponding to the procedure number was not available, it was recorded as “missing”. The following information of a report was extracted: the MAH proposed age variation to update the indication, the benefit-risk assessment (positive, partially positive, or negative), the approved minimum age if the benefit-risk assessment was partially positive, and the application of extrapolation. When an indication included both a procedure with applied extrapolation stud and a procedure without extrapolation, it was categorized as an application of extrapolation. If information in the report was not available, it was recorded as “not specified” or “not applicable”.

Analysis

The collected data will be recorded in a database in Excel, which will facilitate the organization and analysis of the data. All collected data was obtained by two independent reviewers and compared for discrepancies. Analyses will be conducted in R (R version 4.0.3, The R Foundation for Statistical Computing, Vienna, Austria) to summarise all available information.

Results

PIPs eligible for inclusion

The "Table of opinions and decisions on paediatric investigation plans (PIPs)" was downloaded on 25-05-2023. A total of 2602 PIP decisions were recorded in the Excel database (Figure 3). Subsequently, PIP decisions based on the decision type P and PM were selected, which resulted in 1510 PIP decisions meeting the inclusion criteria. Further, selection of the PIP decisions with a compliant PIP yielded 268 PIPs. Out of the 268 PIPs, four were excluded: two PIPs were identified as a duplicate (listed under two different brand names), while two PIPs were omitted due to unavailability of corresponding PIP document on the EMA website. This resulted in 264 (10.1%) PIP decisions included in the analysis.

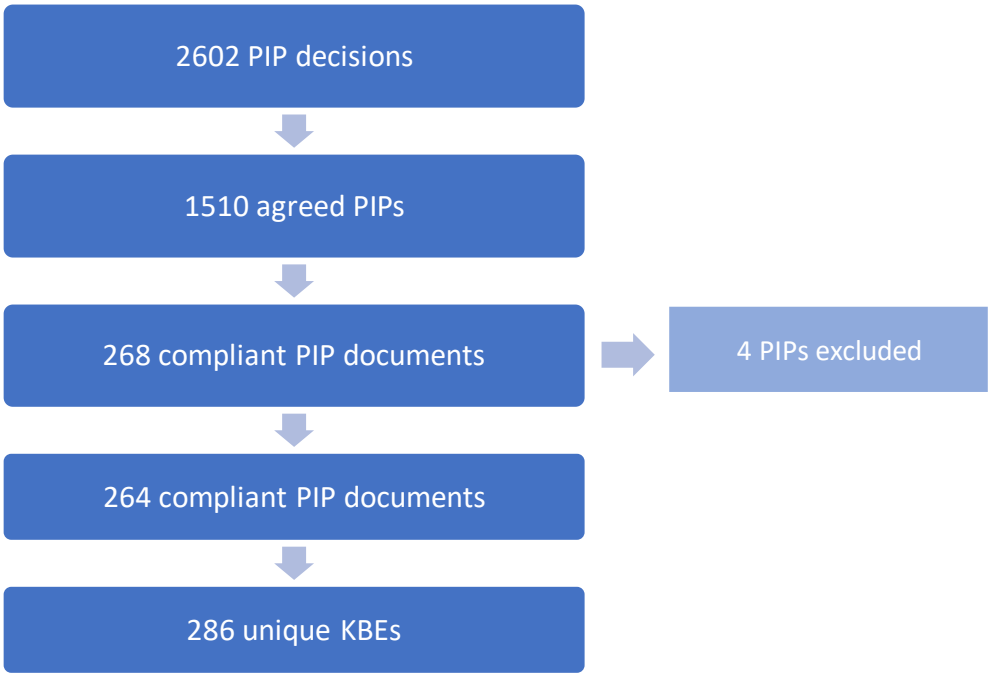

Figure 3. Flow chart of the selection process of unique KBEs eligible for inclusion in this analysis.

Among the 264 PIPs, 38 were classified as P, indicating agreement on the initial investigation plan. Additionally, the compliant PIP belonging to hydrocortisone was classified under the W category in the database system, but actually belonged to the P Category. As a result, 39 PIP decisions (14.7%) were classified as P. Conversely, the majority of the compliant PIPs, accounting for 225 (85.2%), fell under the PM category, representing decisions pertaining to PIPs with one or more modifications from the initially agreed PIP.

Extracted information from PIPs

From the 264 PIPs, a total of 286 unique KBE tables were extracted eligible for analysis.

Key findings in KBEs

Key findings of 286 KBEs regarding the average age, duration to PIP compliance, route of administration, and therapeutic areas for the studied medicinal products are presented (Table 1). The average minimum age specified in the indication of the KBEs was found to be 2.7 years, while the average maximum age was 16.7 years. The average duration to PIP compliance was 4.4 years. Intravenous administration emerged as the most prevalent route of administration (n = 97 (33.9%)). Moreover, the most frequently covered therapeutic area was infectious diseases (n = 38 (13.3%)).

Characteristics of KBEs (N=286)	
Average age (yr)	
Minimum	2.7
Maximum	16.7
Duration to PIP compliance (yr)	
Average	4.4
Minimum	-0.8
Maximum	11.5
Route of administration (3 most prevalent)	N (%)
Intravenous	97 (33.9%)
Subcutaneous	68 (23.8%)
Intramuscular	45 (15.7%)
Other	58 (20.3%)
Therapeutic area (10 most prevalent)	N (%)
Infectious diseases	38 (13.3%)
Oncology	35 (12.2%)
Endocrinology-Gynaecology-Fertility-Metabolism	30 (10.5%)
Immunology-Rheumatology-Transplantation	25 (8.7%)
Vaccines	25 (8.7%)
Haematology-Hemostaseology	24 (8.4%)
Gastroentology-Hepatology	18 (6.3%)
Pneumology-allergology	17 (5.9%)
Neurology	15 (5.2%)
Cardiovascular diseases	11 (3.8%)
Other	48 (16.8%)

Table 1. key findings of 286 KBEs including average age, duration to PIP compliance, route of administration and therapeutic area.

The distribution of study types conducted with each KBE per therapeutic area are found in the appendix (Table S2 – Table S11). No extrapolation studies were conducted within the therapeutic area of vaccines (Table S11).

Study distribution in KBEs

The distribution of the different study types across the 286 KBEs is illustrated (Figure 4). Notably, a majority (95.5%) of the KBEs encompassed at least one clinical study. Additionally, the minority of KBEs included one or more quality studies (33.9%), non-clinical studies (23.1%), and other studies (9.1%). Of particular importance, extrapolation studies were identified in only 16.8% of the KBEs.

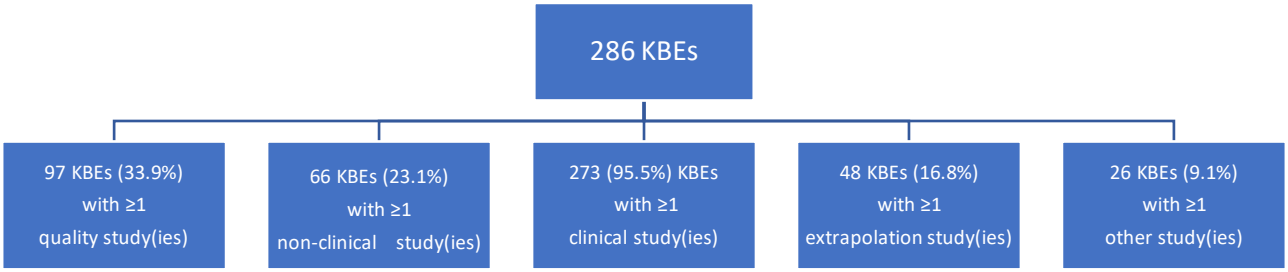

Figure 4. Distribution of 286 KBEs across different study types

Table 2 summarizes the distribution of the number of studies conducted with each KBE, including quality, non-clinical, clinical, extrapolation, and other studies. The table presents the distribution and frequency of studies across 286 KBEs. Regarding clinical studies, a small proportion of 4.5% of KBEs did not include a clinical study. Conversely, in the category of quality, non-clinical, and other studies, the majority of KBEs did not include this type of study. As for extrapolation studies, most KBEs did not include any extrapolation studies. Among the KBEs that did include extrapolation studies, the highest percentage (12.2%) consisted of those conducting one extrapolation study.

Number of studies per KBE (N)	Quality	Non-clinical	Clinical	Extrapolation	Other
0	189 (66.1%)	220 (76.9%)	13 (4.5%)	238 (83.2%)	260 (90.9%)
1	83 (29.0%)	25 (8.7%)	97 (33.9%)	35 (12.2%)	24 (8.4%)
2	13 (4.5%)	23 (8.0%)	66 (23.1%)	10 (3.5%)	1 (0.3%)
3	1 (0.3%)	12 (4.2%)	55 (19.2%)	1 (0.3%)	1 (0.3%)
4+	0 (0.0%)	6 (2.1%)	55 (19.2%)	2 (0.7%)	0 (0.0%)

Table 2. Distribution and frequency of studies (quality, non-clinical, clinical, extrapolation and other) in 286 KBEs

The distribution and characteristics of different study types (quality, non-clinical, clinical, other studies) within the 286 KBEs were analysed to provide insights into the studies within KBEs (Table 3). Among the KBEs, 29.7% included a quality study on new formulations, strengths, and formulation-related aspects, with this type representing 87.6% of all quality studies. Toxicity studies constituted the majority (18.2%) within non-clinical studies, representing a significant portion (78.8%) within that category of studies. Within clinical studies, safety investigations accounted for the largest proportion, comprising 88.8% of the total KBEs, with a significant majority (93.0%) of the clinical studies falling under the category of safety. Other clinical study types, including dose finding, palatability, bioequivalence and immunogenicity accounted for smaller percentages ranging from 3.1% to 15.7%. It is important to note that in some cases, a single clinical study within the KBE encompassed multiple study types, which explains why the total number of KBEs within clinical studies is higher than the total 286 KBEs.

Qualitiy	**KBEs (n (%))**
Development new formulation, strength, etc.	85 (29.7%)
Evalation of appropriatness of current formulation in paediatrics	8 (2.8%)
Other/unknown	5 (1.7%)
Non-clinical	**KBEs (n (%))**
Toxicity	52 (18.2%)
PK	11 (3.8%)
PD or PK/PD	12 (4.2%)
biomarker	3 (1.0%)
Carcinogenicity	1 (0.3%)
Other/unknown	6 (2.1%)
Clinical	**KBEs (n (%))**
PK	160 (55.9%)
PD	69 (24.1%)
Efficacy	192 (67.1%)
Safety	254 (88.8%)
Dose finding	45 (15.7%)
Immunogenicity	38 (13.3%)
Palatability	9 (3.1%)
Bioequivalence	31 (10.8%)

Table 3. distribution of categories in different study types within 286 KBEs.

To provide more insights into different extrapolation study types, the extrapolation studies are divided into different categories for type and aim (Table 4). The distribution of studies related to extrapolation revealed that most of extrapolation type studies fell under the category of other or unknown (56.7%). Among the defined extrapolation types, the most common were population pharmacokinetic (POP-PK) studies (19.4%) and population PK/PD studies (10.4%). Similarly, when considering the aim of extrapolation studies, a considerable proportion (38.8%) fell under the category of other or unknown, while efficacy studies represented the largest proportion (32.8%).

Extrapolation type (N=67)	N (%)
POP-PK	13 (19.4%)
POP-PK/PD	7 (10.4%)
Silico	1 (1.5%)
PBPK	6 (9.0%)
POP-PK + exposure-response	1 (1.5%)
Exposure-response	1 (1.5%)
Other/unknown	38 (56.7%)
Extrapolation aim (N=67)	N (%)
PK	8 (11.9%)
PK/PD	1 (1.5%)
Dose-finding	10 (14.9%)
Efficacy	22 (32.8%)
Other/unknown	26 (38.8%)

Table 4. Distribution of extrapolation studies in different categories, divided in 'type' and 'aim'.

Extracted information from SmPC's

Indications in KBEs

Out of the initial 286 KBEs, 59 were found to have no SmPC, leaving 227 KBEs corresponding to 238 indications suitable for analysis (Figure 5).

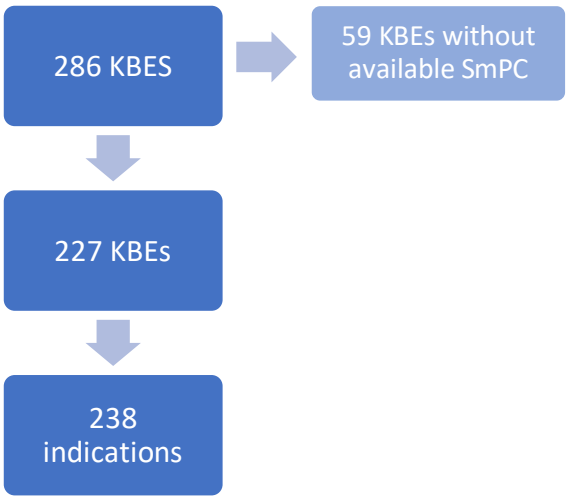

Figure 5. Flow chart of the selection process of indications eligible for inclusion in analysis.

Approved indications of KBEs

Out of the 238 indications, 151 indications were fully approved, 44 indications were partially approved, and 43 indications were not approved (Figure 6). Within the fully approved indications, 24 had an expanded age range in the SmPC compared to the initially submitted range in the KBE. Additionally, 58 (24.4%) out of the 238 indications received approval for the complete paediatric indication spanning from 0 to 18 years.

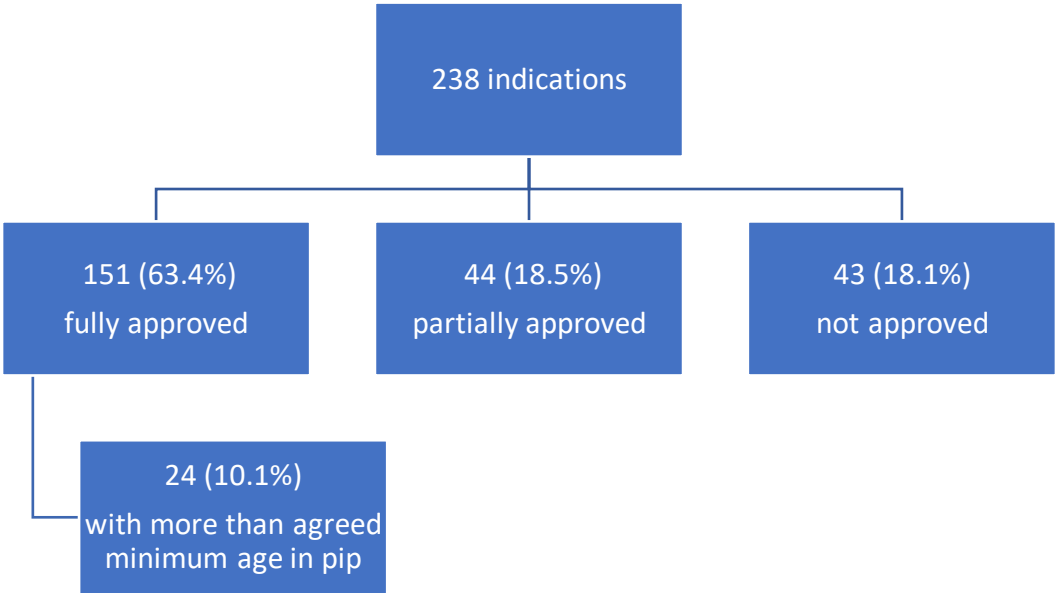

Figure 6. Distribution of marketing approval among 238 indications.

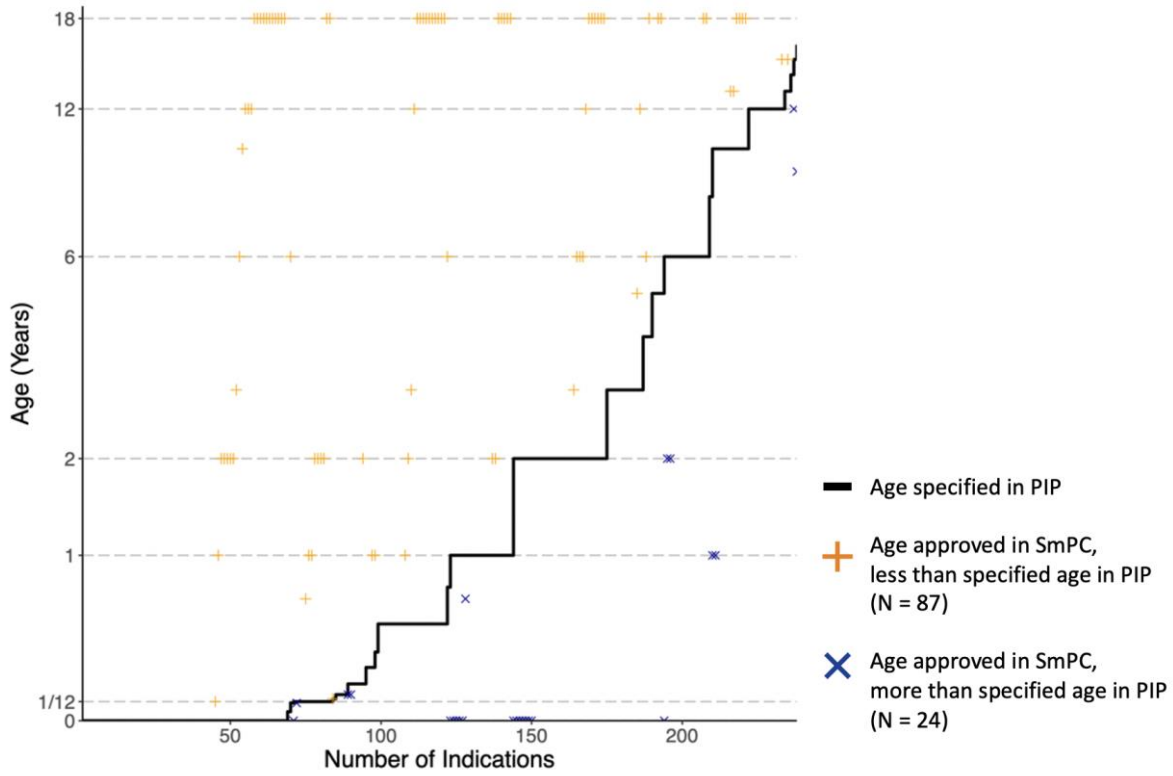

Figure 7 illustrates the distribution of approved indications based on the minimum age specified in the PIP and the minimum age in the SmPC. The orange crosses on the line at 18 years represents the indications that were not approved (N = 43). The orange crosses below the line at 18 years indicate partially approved (N = 44). The blue crosses represent indications that were approved beyond the agreed minimum age in the PIP (N = 24).

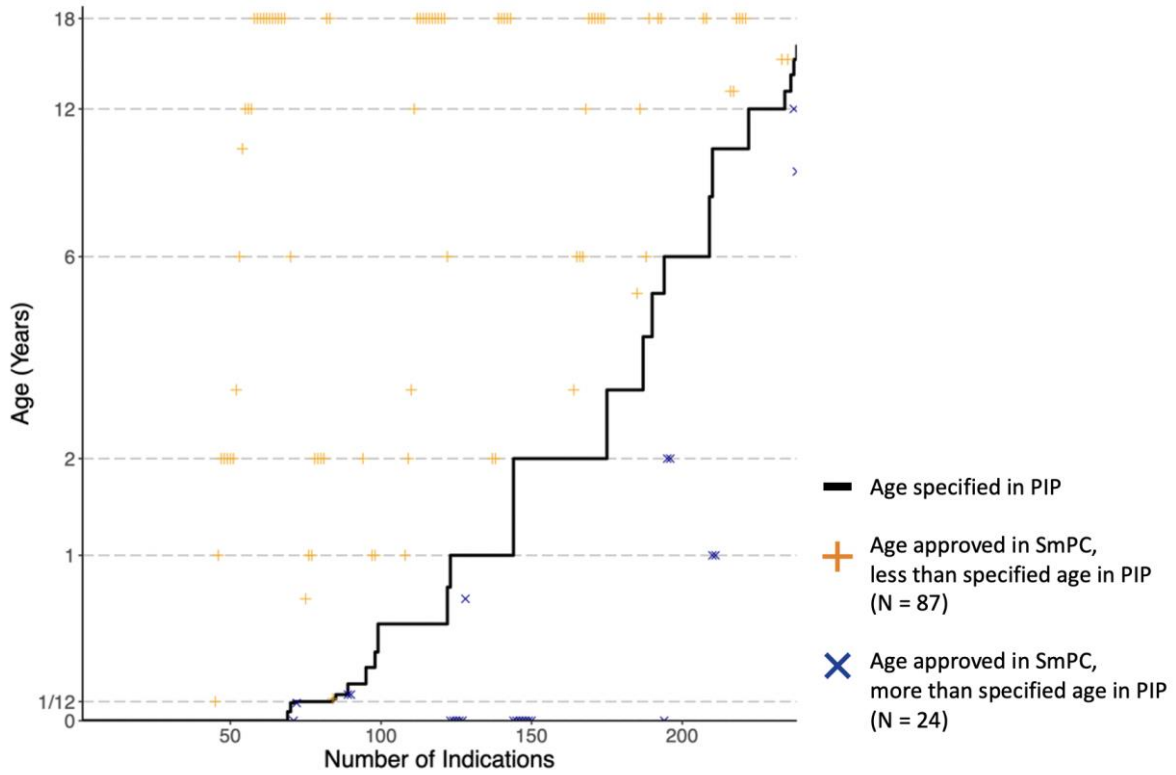

Figure 7. Distribution of approved indications by representing the minimum age specified in the PIP and the minimum age approved in the SmPC of 238 indications. The orange crosses represent the minimum age approved in the SmPC, which was less than the agreed minimum age in the PIP. In contrast, the blue crosses represent the minimum age approved in the SmPC, which was more than the agreed minimum age in the PIP. If the minimum age approved in the SmPC was similar to the minimum age in the PIP, these observations were omitted from the graph.

Figure 8 represents the average trend of the minimum age specified in the PIP and the minimum age in the SmPC. The orange line would align with the black line if all minimum ages specified in the PIP were approved in accordance with the SmPC. However, the average trend indicates that the minimum age applied in the PIP is lower than the minimum age approved in the SmPC.

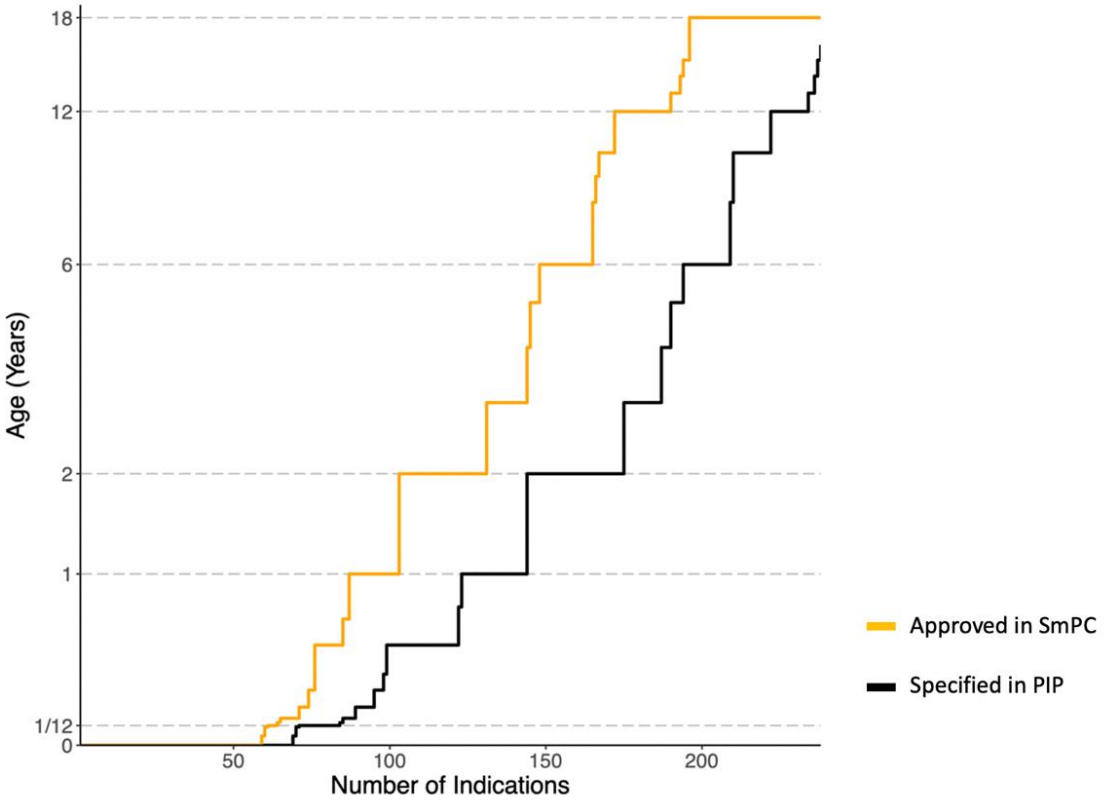

Figure 8. Average trend of the minimum age applied in the PIP and minimum age approved the SmPC of 238 indications. The orange line represents the approved minimum age in the SmPC and the black line represents the minimum age specified in the PIP.

Extracted information from the EPAR

Indications in procedures

Out of the 238 requested indications, 36 indications did not have an available documentation of the procedure, resulting in 202 indications with available information on marketing approval (Figure 9).

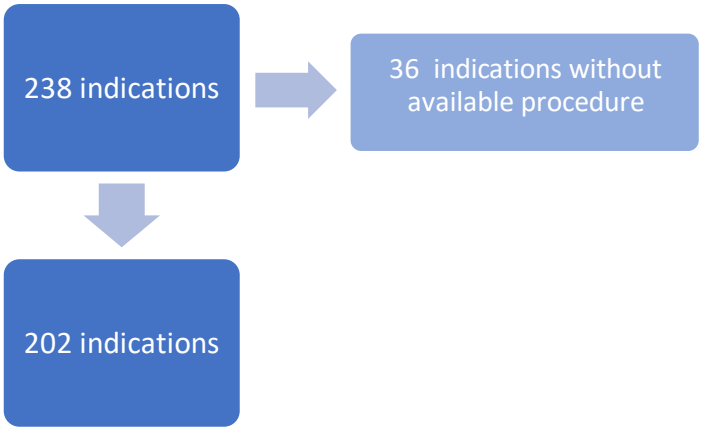

Figure 9. Flow chart of the selection process of indications eligible for inclusion in analysis.

Role of extrapolation

Out of the 202 indications with available documentation on marketing approval, 72 (35.6%) applied extrapolation and 130 (64.4%) did not apply extrapolation (Table 5).

Extrapolation	**Indication (N (%))**
No	130 (64.4%)

Yes	72 (35.6%)
Total	202

Table 5. Distribution of the application of extrapolation in 202 indications.

The average minimum age approved is 5.2 years and 3.8 years in indications that did not use an extrapolation approach during marketing application versus indications that did, differing by 1.4 years compared (Table 6). When extrapolation is not applied, the average age specified in the PIP is 2.0 years, differing by 3.2 years compared to the average age of 5.2 years approved in the SmPC. Conversely, when extrapolation is applied, both the average age specified in the PIP and the average age approved in the SmPC are 3.8 years.

Extrapolation	Average age specified in PIP (years)	Average age approved in SmPC (years)
No	2.0	5.2
Yes	3.8	3.8

Table 6. Average minimum age specified in PIP and average minimum age approved inSmPC with or without extrapolation in 202 indications.

The average duration for PIP compliance is 4.8 years without applying extrapolation, differing by 0.6 years compared to the average duration of 5.4 years with applying extrapolation (Table 7).

Extrapolation	Average duration for PIP compliance (years)
No	4.8
Yes	5.4

Table 7. Average duration of PIP to become compliant with or without extrapolation in 202 indications.

Figure 10 represents the average trend of the minimum age specified in the PIP and the minimum age in the SmPC, stratified by the utilization of extrapolation. When extrapolation is applied, the alignment between the orange and black lines is greater compared to when no extrapolation is applied, suggesting a higher level of approval for the minimum age specified in the PIP. Moreover, the utilization of extrapolation increases the frequency of approvals exceeding the minimum age specified in the PIP, in contrast to cases without extrapolation.

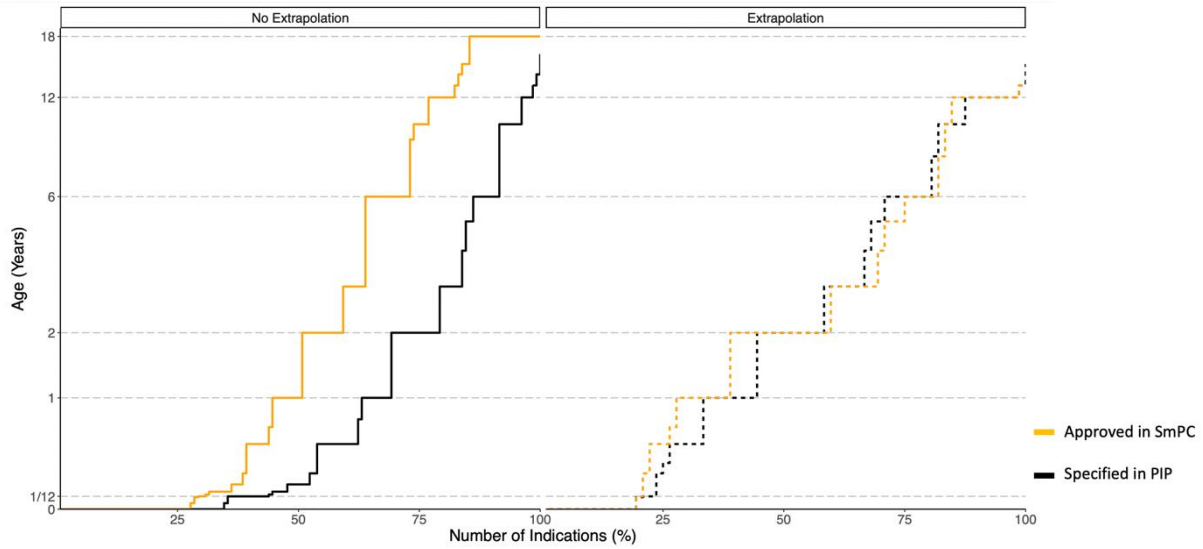

Figure 10. Average trend of the minimum age applied in the PIP and minimum age approved the SmPC of 238 indications stratified by extrapolation (yes/no).

Examples of paediatrics as reference population

Several medicinal products have applied paediatric extrapolation, using paediatrics as reference population (Table 8).

Medicinal product	Indication	Target population	Reference population	Extrapolation type
			Adults	Full
		Paediatrics (4 – 16 years)		
	Epilepsy with partial-onset seizures		Paediatrics (4 - 18 years) + adults	Full
Lacosamide		Paediatrics (2 - 4 years)		
			Paediatrics (4 - 18 years) + adults	Partial
Rufinamide	Lennox-Gastaut syndrome	Paediatrics (1 - 4 years)		
			Paediatrics (12 - 18 years) + adults	Full
Insulin detemir	Diabetes type 2	Paediatrics (1 - 5 years)		
				Partial
Adalimumab	Polyarticular juvenile idiopathic arthritis	Paediatrics (2 - 4 years)	Paediatrics (4 – 12 years)	
				Partial
Anakinra	Systemic juvenile idiopathic arthritis	Paediatrics (0.67 – 2 years)	Paediatrics (2 - 18 years)	
	Treatment and prevention of influenza.		Paediatrics (1 -18 years) + adults	Full
Oseltamivir		Paediatrics (0 - 1 years)		

Table 8. Examples of medicinal products that applied paediatric extrapolation using paediatrics as reference population.

Discussion

Since the introduction of the paediatric regulation in 2007 up until 2022, 10.1% of the PIPs have been concluded as compliant. A total of 16.8% of unique KBEs were supported by extrapolation studies. These extrapolation studies aimed to assess efficacy, pharmacokinetics (PK), pharmacokinetics/pharmacodynamics (PK/PD), and dose-finding, primarily utilizing POP-PK approaches. Furthermore, it was observed that 35.6% of the indications applied extrapolation, which is almost twice the percentage observed in the KBEs. The application of extrapolation results in a difference of 1.4 years in the average minimum approved age compared to when extrapolation is not applied. Without extrapolation, there is a difference of 3.2 years between the average minimum age specified in the PIP and the average minimum age approved in the SmPC, whereas with extrapolation, both averages align at 3.8 years.

PIPs eligible for inclusion:

Among the 2602 extracted PIP decisions, only 268 (10.2%) were found to be compliant. The majority of compliant PIPs, amounting to 225 cases (84.9% of the total), were categorized as PM. This implies that only 15.1% of the 265 compliant PIPs did not undergo modifications after the initial agreed investigation plan. This relatively low number of compliant PIPs could indicate that paediatric drug development still faces many challenges. Modifications of the initially agreed PIP may be necessary for various reasons.[13] For example, an applicant may deviate from their original plan by submitting an application for multiple conditions simultaneously, instead of seeking authorization for only one condition as initially intended. Conversely, they may choose to pursue authorization for a single condition, departing from the initial plan of multiple conditions. However, feasibility of some of the requirements specified in the key binding elements table may also contribute to this finding.

Extracted information from PIPs:

Out of the 264 compliant PIPs, a total of 286 unique KBE tables were identified. The average minimum age specified in the indication of the KBEs was 2.7 years. It should be noted that the age group of infants and toddlers (0-2 years) was often not included in the specified age range of the PIPs. This exclusion of the 0-2 age group from the PIPs may result in a continued therapeutic orphan status for this specific population, as their specific needs are many and potential treatment options remain limited.

One of the most important findings is that only a limited number of studies within the KBEs were explicitly defined as extrapolation studies. This questions the role of extrapolation in paediatric drug development. For the majority of unique KBEs that did specify an extrapolation study, the exact type and aim could not be identified from the publicly availability information. This indicates a need for further clarification of the role of paediatric application in publicly available PIPs. It is important to recognize that the information initially provided in the PIP may not explicitly mention or define the utilization of extrapolation methodologies. Upon further analysis of the individual study reports, it became apparent that more than twice as many studies employed an extrapolation approach. These findings underscore the need for improved and more explicit documentation of the approach used for paediatric drug development (i.e. extrapolation used and extent of extrapolation). Enhancing the reporting and categorization of such studies in future PIPs would facilitate a better understanding of the extent and impact of extrapolation in paediatric drug development and would allow publicly funded researchers to step in. By clearly defining and acknowledging the utilization of extrapolation methodologies, researchers and regulatory bodies can enhance transparency, reproducibility, and the overall quality of paediatric clinical research.

Extracted information from SmPCs:

Out of the 238 indications that were pursued in the unique KBEs, 63.4% were fully approved, while 18.5% received only partial approval, and 18.1% of indications were not approved at all. These findings highlight the need for improvements in the PIPs to ensure a higher rate of successful approvals of paediatric marketing applications as the current age range specified in the PIP supports the needs for approval. Efforts should be made to increase the understanding of regulatory requirements and optimize the PIP to ensure that submitted indications are more likely to achieve full approval. Collaboration between regulators, pharmaceutical companies and researchers is crucial in addressing the challenges associated with achieving full approvals for paediatric indications.

Extracted information from EPARs:

In this study, it is observed that within indications where extrapolation was applied, the average minimum approved age range in the SmPC is 1.4 years lower compared to when no extrapolation was applied. When extrapolation is not applied, there is a difference of 1.8 years between the average age specified in the Paediatric Investigation Plan (PIP) and the average age approved in SmPC. However, with the application of extrapolation, the minimum age specified in the PIP and approved in the SmPC are both 3.8 years, indicating no discrepancy. This suggests that extrapolation enables a more consistent alignment between the planned age specified in the PIP and the age approved in the SmPC. The drawback is that the duration of PIP compliance is 0.6 years longer for studies that utilized extrapolation compared to those without extrapolation. This was unexpected as extrapolation studies are often shorter in duration and allow inclusion of less patients compared to efficacy studies. However, this finding can presumably be attributed to a lower approved minimum age in the SmPC when an extrapolation is applied. Paediatric drug development that relies on clinical studies could for example terminate early due to a lack of apparent efficacy, while these findings may be biased by maturation factors that are not account for in traditional study design.

While our analysis showed that 35.6% of the indications applied extrapolation, the FDA's recent publication on paediatric drug labelling changes from 2015 to 2021 found that 63.8% of the labelling changes involved an extrapolation approach. The difference in the use of extrapolation between the EMA and the FDA can be attributed to several factors. First, it is important to realize that the EMA and the FDA are using different regulatory frameworks and guidelines, which might affect their approach to extrapolation. Variations in regulatory requirements, data standards and interpretations of scientific evidence may contribute to differences in the frequency and acceptance of extrapolation at the two agencies. Another possible explanation for this finding is the different time frames examined. While the FDA focused on the period from 2015 to 2021, our study had a broader time frame starting from 2007. This could contribute to variations in frequency of extrapolation, as more recent procedures could have a higher frequency of extrapolation studies. Focusing on different types of data is another possible factor contributing to the difference. Our study relied specifically on publicly available data, which could introduce limitations and biases. The limitation to publicly available information could result in a relatively higher percentage of missing data, potentially affecting the overall representation of the use of extrapolation. In contrast, FDA's analysis of labelling changes may have included a wider range of data sources, potentially providing a more comprehensive view of the use of extrapolation. Finally, our study focussed on compliant PIPs. Non-compliant PIPs that have ongoing clinical trials already file marketing applications for older paediatric patients, where sufficient evidence of the benefit/risk balance is already achieved.

The results of this study however highlight that extrapolation is quite successful in achieving approval in the intended paediatric population. The utilization of extrapolation is driven by its advantages in addressing practical constraints encountered in paediatric clinical studies. Successful application of extrapolation relies on three main assumptions (disease, pharmacology and clinical response

similarity). Paediatric drug development could thus benefit from investigating the plausibility of these findings, which will allow more extrapolation approaches for new medicinal products.

Limitations

Our study has several limitations. The minimum duration of PIP compliance was -0.8 years, which can be explained by the delay in the publication of data by the EMA. This delay caused a time lag between the compliance opinion and its official publication, resulting in a duration that appears shorter than expected. This highlights the need to consider this factor when interpreting the results of duration of a PIP compliance. It is however expected that this bias occurs at random and therefore affect both paediatric marketing applications based on extrapolation and those not based on extrapolation. Another limitation relates to the restriction to publicly available information, which resulted in a relatively high rate of missing data, particularly in the EPAR. Moreover, procedures often did not clearly indicate whether extrapolation had been applied or not. To address this issue, data availability and reporting practices need to be improved. Efforts are needed to enhance the transparency and completeness of information and ensure the use of extrapolation is clearly documented and easily identifiable. This will contribute to more comprehensive and reliable analyses in future research, leading to a better knowledge of the use and impact of extrapolation in paediatric drug development.

Conclusions

Only a limited number of PIPs are currently considered compliant by the PDCO. Interestingly, the mean minimum age specified in the indication of the KBEs was 2.7 years, and the exclusion of the 0-2 years age group from the PIPs raises concerns about the continued therapeutic orphan status for this specific population.

The role of paediatric extrapolation appears to be limited in publicly available paediatric investigation plans. However, from the marketing application procedures, it is apparent that paediatric extrapolation has a more pronounced role in the approval of paediatric indications. Additionally, the aim of the proposed extrapolation study was often not clearly specified. This discrepancy suggests a possible lack of clear specification in PIP on the approach used to collect sufficient evidence in the paediatric population to determine the benefit/risk.

Interestingly, procedures that used extrapolation have a lower approved minimum age compared to procedures that did not use extrapolation. In addition, paediatric extrapolation procedures resulted, on average, in the same approved age range as planned in the paediatric investigation plans. These findings imply that the use of paediatric extrapolation could translate in broader approved paediatric age range and could therefore reduce off-label use. The longer average duration observed in extrapolation should not only be seen as a disadvantage, but rather reflects the suitability and validity of obtaining sufficient information in the paediatric population across a wider age range.

Future investigations should aim to assess the proportions of fully, partially, and not approved indications when extrapolation is employed or not, as well as examine the specific age groups and types of extrapolation utilized. Such research would provide valuable insights for regulatory decision-making, refine the use of extrapolation, and optimize the design of paediatric clinical trials based on compliance with the three key assumptions of disease similarity, pharmacology similarity, and clinical response similarity outlined in established procedures.

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Supplemental information:

	Age
Preterm newborn infants	0 years
Term newborn infants	0 – 27 days
Infants and toddlers	28 days - 23 months
Children	2 – 11 years
Adolescents	12 to 16-18 years

Table S1. age groups according to ICH guideline.

	Number of study types per KBE				
Study types	**0**	**1**	**2**	**3**	**4+**
Clinical	0	1	6	2	2
Non-Clinical	7	1	3	0	0
Extrapolation	9	2	0	0	0
Other	10	1	0	0	0
Quality	5	5	1	0	0

Table S2. Distribution and frequency of studies in the therapeutic area Cardiovasculair in 286 KBEs.

Study types	Number of study types per KBE				
	0	**1**	**2**	**3**	**4+**
Clinical	0	7	10	8	5
Non-Clinical	24	2	3	0	1
Extrapolation	24	3	3	0	0
Other	29	1	0	0	0
Quality	22	8	0	0	0

Table S3. Distribution and frequency of studies in the therapeutic area Endocrinology-Gynaecology-Fertility-Metabolis in 286 KBEs.

Study types	Number of study types per KBE				
	0	**1**	**2**	**3**	**4+**
Clinical	1	12	0	4	1
Non-Clinical	15	2	0	1	0
Extrapolation	14	4	0	0	0
Other	16	2	0	0	0
Quality	14	4	0	0	0

Table S4. Distribution and frequency of studies in the therapeutic area Gastroentology-Hepatology in 286 KBEs.

Study types	Number of study types per KBE				
	0	**1**	**2**	**3**	**4+**
Clinical	1	1	5	8	9
Non-Clinical	23	1	0	0	0
Extrapolation	22	2	0	0	0
Other	23	0	1	0	0
Quality	15	7	2	0	0

Table S5. Distribution and frequency of studies in the therapeutic area Haematology-Hemostaseology in 286 KBEs.

Study types	Number of study types per KBE				
	0	**1**	**2**	**3**	**4+**
Clinical	1	14	5	1	4
Non-Clinical	20	1	1	2	1
Extrapolation	20	5	0	0	0
Other	22	3	0	0	0
Quality	18	7	0	0	0

Table S6 Distribution and frequency of studies in the therapeutic area Immunology-Rheumatology-Transplantation in 286 KBEs.

Study types	Number of study types per KBE				
	0	**1**	**2**	**3**	**4+**
Clinical	2	10	14	7	5
Non-Clinical	27	3	3	5	0
Extrapolation	29	8	1	0	0
Other	38	0	0	0	0
Quality	17	15	6	0	0

Table S7. Distribution and frequency of studies in the therapeutic area Infectious diseases in 286 KBEs.

Study types	Number of study types per KBE				
	0	**1**	**2**	**3**	**4+**
Clinical	0	9	4	1	1
Non-Clinical	10	2	2	0	1
Extrapolation	13	1	0	0	1
Other	12	3	0	0	0
Quality	7	7	0	1	0

Table S8. Distribution and frequency of studies in the therapeutic area Neurology in 286 KBEs.

Study types	Number of study types per KBE				
	0	**1**	**2**	**3**	**4+**
Clinical	2	18	6	6	3
Non-Clinical	19	9	4	1	2
Extrapolation	26	5	4	0	0
Other	32	3	0	0	0
Quality	29	6	0	0	0

Table S9. Distribution and frequency of studies in the therapeutic area Oncology in 286 KBEs.

Study types	Number of study types per KBE				
	0	**1**	**2**	**3**	**4+**
Clinical	1	7	2	1	6
Non-Clinical	14	0	0	3	0
Extrapolation	12	4	0	0	1
Other	16	1	0	0	0
Quality	10	5	2	0	0

Table S10. Distribution and frequency of studies in the therapeutic area Pneumology-allergology in 286 KBEs.

Study types	Number of study types per KBE				
	0	**1**	**2**	**3**	**4+**
Clinical	1	3	3	6	12
Non-Clinical	24	1	0	0	0
Extrapolation	25	0	0	0	0
Other	24	0	0	1	0
Quality	21	3	1	0	0

Table S11. Distribution and frequency of studies in the therapeutic area Vaccines in 286 KBEs.