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ORIGINAL ARTICLE

A review on the role of extrapolation as basis for paediatric marketing authorization applications of medicines in the EU

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Aims: For new medicines, drug companies obtain regulatory approval on the strategy to generate evidence in the paediatric population, which can be supported by extrapolation of evidence obtained in a reference population. This study investigated whether paediatric marketing authorization applications (PMAAs) supported by extrapolation based on exposure-matching were more successful—i.e. approval of the targeted paediatric population—and efficient—i.e. duration of the drug development—compared to PMAAs not supported by extrapolation.

Methods: Data was extracted from completed paediatric investigation plans (PIPs), associated drug labels and public assessment reports published on the European Medicines Agency website. Assessment reports were evaluated to assess whether PMAAs were supported by extrapolation based on exposure-matching. Wilcoxon rank-sum tests were used to compare PMAAs supported and not supported by extrapolation based on exposure-matching for outcomes of interest.

Results: Exposure-matching supported the benefit/risk assessment of 39.6% of the PMAAs. Targeted and approved minimum age of the paediatric population were comparable for PMAAs where extrapolation based on exposure-matching supported the benefit/risk assessment (2.0 *vs*. 2.0 years, *P*-value = .72), but not for PMAAs not supported by extrapolation (0.2 years *vs*. 0.5 years, *P*-value = .05). Completion of drug development was 5.4 years *vs*. 4.3 years (*P* = .04) in PMAAs supported by extrapolation based on exposure-matching compared to those not supported by extrapolation, respectively.

Conclusions: PMAAs supported by extrapolation based on exposure-matching succeeded more often in obtaining marketing approval in the targeted paediatric population than PMAAs not supported by exposure-matching, but were also less efficient.

KEYWORDS
drug development, extrapolation, paediatric medicine, pharmacometrics, regulatory science

1 | INTRODUCTION

Upon marketing authorization application, drug companies are required to provide evidence to regulatory authorities that demonstrates whether a new medicinal product can be considered effective, safe and of good quality. Generation of evidence in the paediatric population is often hampered by difficulties in conducting clinical trials.[1] For example, paediatric clinical trials face ethical challenges, a diverse population, therefore requiring a larger sample size to demonstrate therapeutic benefit, a limited number of validated clinical endpoints and a limited possibility to collect biological specimens.[2] Generation of evidence in the paediatric population to a similar extent as the adult population is therefore often unrealistic. Consequently, obtaining marketing authorization in the paediatric population is more difficult and off-label use of medicines in this population remains high.[3–5]

In the European Union (EU), the paediatric regulation (Regulation 1901/2006 and 1902/2006) aims to reduce off-label use in the paediatric population by requiring drug companies to submit a paediatric investigation plan (PIP) before approval of the adult indication can be obtained.[6] In a PIP, drug companies propose a strategy to generate sufficient evidence to assess whether a medicinal product can be considered effective, safe and of good quality in the targeted paediatric population.[6] The PIP needs to be agreed upon by the paediatric committee (PDCO) of the European Medicines Agency (EMA). Results of studies described in the agreed PIP need to be included in marketing authorization applications for new medicinal products but also extension of indications of existing medicinal products unless a deferral (i.e., delay in initiation or completion of drug development programme) or a waiver (i.e., lack of requirement to study a [part of the] paediatric population) is granted.[7] A drug company can apply for marketing authorization in the targeted paediatric population when sufficient evidence is generated. Following a marketing authorization application by a drug company, the Committee for Medicinal Products for Human Use (CHMP) will assess whether the medicinal product is of good quality and whether the benefits of the medicinal product outweigh the risks in the targeted population. If so, marketing authorization is granted. The quality and benefit/risk assessment of the CHMP is published upon marketing authorization in public assessment reports.

Evidence generation in the targeted paediatric population can be supported by extrapolation of evidence that has already been obtained in a reference population (e.g., adult population with same disease or paediatric population with different disease).[8,9] This concept is known as paediatric extrapolation. As reflected in regulatory guidance documents, extrapolation of efficacy can be limited to generation of evidence that demonstrates similar drug exposure in the paediatric target and reference population, when the mechanistic basis of the disease, exposure–response relationships and treatment effects in the target and reference populations are expected to be similar.[8,9] In this study, this will be referred to as extrapolation based on exposure-matching.

This study aimed to investigate how often extrapolation based on exposure-matching is agreed upon by the PDCO as a strategy to be used for evidence generation in the paediatric population. This study also aimed to investigate how often regulatory authorities used this evidence as support for the assessment of the benefit/risk balance in paediatric marketing authorization applications. Finally, this study aimed to evaluate whether paediatric marketing authorization applications supported by extrapolation based on exposure-matching were more successful, in terms of approval of the targeted paediatric population in the PIP, and more efficient, in terms of the time for completion of the paediatric drug development programme, compared to paediatric marketing authorization applications that did not use extrapolation based on exposure-matching.

What is already known about this subject

- Approximately 64% of the paediatric marketing authorization applications of medicines between 2015 and 2021 reviewed by the US Food and Drug Administration used some form of extrapolation.
- The question whether paediatric marketing authorization applications, in which the benefit/risk assessment is supported by extrapolation based on exposure-matching, more successful, in terms of approval of the targeted paediatric population, and more efficient, in terms of duration of completion of the drug development program, is addressed.

What does this study adds

- Paediatric marketing authorization applications of medicines supported by extrapolation based on exposure-matching are more successful in terms of approval of the targeted paediatric population than traditional approaches in the EU, but are also less efficient.
- Based on this research, it is recommended to explicitly state questions to-be-answered in planned drug development programs and how these questions are expected to contribute to the benefit/risk discussion for the targeted paediatric population. This is expected to clarify the goals and assumptions of the paediatric drug development, stimulate research and may increase the number of marketing applications eligible for an extrapolation approach based on exposure-matching.

2 | METHODS

2.1 | Role of extrapolation in PIPs

First, the number of PIPs where extrapolation based on exposure-matching was agreed upon by the PDCO as a strategy for evidence

generation in the paediatric population was extracted. A dataset concerning PDCO opinions and decisions on PIPs is publicly available and can be downloaded from the EMA website (https://www.ema.europa.eu/en/medicines/download-medicine-data#paediatric-investigation-plans-section). The non-confidential part of each individual PIP document can be accessed at the EMA website. In each of these publicly-available PIP documents, a number of key binding elements (KBEs) is specified in one or more KBE tables. Specific studies that need to be performed by drug companies to be able to assess the benefit/risk balance of a medicinal product in the targeted paediatric population are specified in the KBE tables.[7] Compliance checks of the KBEs are performed by the EMA to evaluate whether a drug company is generating evidence in accordance with the agreed PIP. After completion of all studies specified in the KBE tables, a PIP is considered compliant by the EMA. Compliant PIP documents were eligible for inclusion in this analysis, but duplicate PIP documents (i.e., same product, same therapeutic indication/condition, same formulation) were excluded.

A PIP document can contain multiple unique KBE tables, because each PIP document can cover multiple therapeutic indication(s). Additionally, each unique KBE table can be associated with one or more therapeutic indication(s) with the same specific study requirements (e.g., for deferasirox [EMEA-C-001103-PIP01–10-M03], three therapeutic indications are specified in the PIP, but only one KBE table is specified). A unique KBE table associated with one or more therapeutic indication(s) was considered as a unique paediatric drug development programme in this study.

From the PIP documents, all unique KBE tables and targeted paediatric population (i.e., associated therapeutic indication(s) and age range(s)) were extracted. When available, the aim of the tabulated studies was extracted. For extrapolation studies, the type of study was also extracted. All data extractions were performed by two independent researchers (J.V.K. and C.W.M.S.) for the entire analysis. In case of discrepancies between the two researchers, documents were jointly reviewed.

2.2 | Data extraction from the drug label

Second, to investigate whether paediatric drug development programmes specified in compliant PIPs resulted in marketing authorization of a medicinal product in the targeted paediatric population, restrictions from use of the medicinal product in the paediatric population were extracted from the approved therapeutic indication in the drug label (i.e., section 4.1 of the Summary of Product Characteristics [SmPC]), i.e., specification of a minimum age and, if applicable, minimum bodyweight. This was done for all therapeutic indications associated with a KBE table.

The targeted minimum age specified in compliant PIPs was compared to the approved minimum age specified in the drug label and categorized as: fully approved, when the minimum age in the drug label was similar to the minimum age specified in the PIP; more than fully approved, when the minimum age in the drug label was lower than the minimum age specified in the PIP; partially approved, when the minimum age in the drug label was higher than the minimum age specified in the PIP; or not approved, when the paediatric indication was not granted. If drug labels were not found on the EMA website, it was assumed that no paediatric indication was requested by a drug company.

2.3 | Exposure-matching as support for the benefit/risk assessment

Third, we evaluated whether exposure-matching was used to support the CHMP assessment of the benefit/risk in public assessment reports of paediatric marketing authorization applications associated with the therapeutic indications specified in the compliant PIPs. All paediatric marketing authorization applications were considered where drug companies applied for a new paediatric indication or extension of an already approved paediatric indication. Furthermore, extrapolation based on exposure-matching was defined as a quantitative comparison of similarity in pharmacokinetics or pharmacokinetics-pharmacodynamics between the targeted paediatric population and a reference population (e.g., adult patients or other paediatric patient population) discussed as supportive evidence of efficacy in the benefit/risk discussion section of the assessment report. In case the benefit/risk discussion section was missing, the discussion sections around pharmacology and efficacy were evaluated instead.

Subsequently, paediatric marketing authorization applications where exposure-matching supported the assessment of the benefit/risk discussion were compared against those where exposure-matching was not used to support the assessment of the benefit/risk discussion. Characteristics that were compared were for efficiency; duration for obtaining PIP compliance and number of PIP modifications, and for success; restrictions in use of the medicinal product in the targeted paediatric population as specified in the drug label and PIP: minimum bodyweight, age groups and minimum age.

Additional subgroup analyses were conducted per therapeutic area, orphan disease status and small *vs*. large molecules. For this, orphan disease status was extracted from the 'community register of orphan medicinal products' published on the European Commission website (https://ec.europa.eu/health/documents/community-register/html/reg_od_act.htm?sort=a) for each therapeutic indication. Additionally, molecular size was used to distinguish between small and large molecules, in which a small molecule was defined as ≤1000 g/mol.

2.4 | Analysis

For both the PIP as well as the drug label, when an age group was specified in the therapeutic indication instead of a minimum age, the minimum age was assumed to be aligned with the age group definition of the ICH E11 Guideline. Additionally, age groups in the analysis were also defined according to the ICH E11 Guideline: newborn infants (0 to < 1 month), infants or toddlers (1 month to < 2 years), children (2 to < 12 years) or adolescents (12 to < 18 years).[10] For feasibility reasons, if "age of menarche" was specified in the PIP or drug label, the minimum age was imputed as 12 years. When the PIP or drug label did not provide a minimum age or minimum bodyweight, it

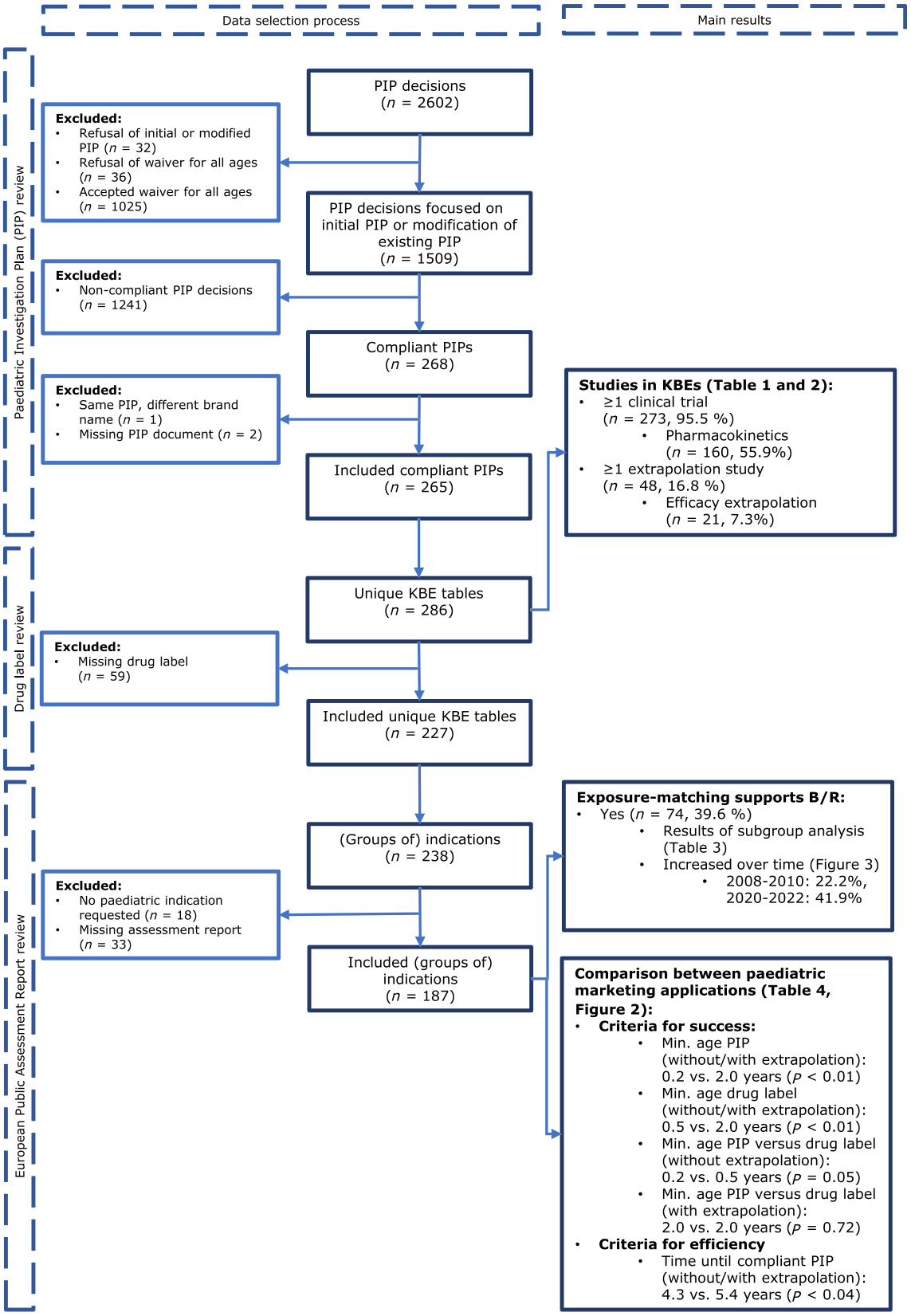

FIGURE 1 Flowchart of included paediatric investigation plan documents, unique key binding element tables and (groups of) indications and summary of results.

was assumed that the medicinal product was authorized for use in the full paediatric population.

Generally, descriptive statistics were used to summarize all findings. Comparisons for continuous outcomes, such as the minimum age specified in the drug label, were conducted using the Wilcoxon rank-sum test. Comparisons for categorical outcomes, such as approval of different age groups, were conducted using the Pearson's Chi square test. For both tests, a *P*-value less than .05 was considered statistically significant. All analyses were conducted using R version 4.0.3 (R core team, Vienna, Austria) and stats package version 3.6.2.

3 | RESULTS

3.1 | Role of extrapolation in PIPs

The extracted PIP dataset, downloaded on 25 May 2023, contained 2602 PIP decisions that were first published between 20 December 2007 and 11 May 2023. A total of 1509 of the 2602 PIP concerned decisions on an agreed initial PIP or a modification of the agreed initial PIP. Of these, 268 (17.8%) PIP decisions were listed as compliant and individual PIP documents were extracted from the EMA website. Three PIPs were excluded: one was considered a duplicate (same active substance, formulation and condition, but a different brand name) and two were not published on the EMA website and therefore considered missing. A flowchart summarizing the inclusion and exclusion of PIPs is provided in Figure 1.

The resulting 265 (17.6%) PIP decisions were first published between 19 March 2008 and 22 June 2021. The most frequently covered therapeutic areas were infectious diseases ($n = 38$, 13.3%), oncology ($n = 35$, 12.2%), endocrinology-gynaecology-fertility-metabolism ($n = 30$, 10.5%), vaccines ($n = 25$, 8.7%), immunology-rheumatology-transplantation ($n = 25$, 8.7%), haematology-haemostaseology ($n = 24$, 8.4%), pneumology-allergology ($n = 17$, 5.9%), gastroenertology-hepatology ($n = 17$, 5.9%) and neurology (n = 15, 5.2%).

From the 265 PIP documents included in this analysis, 286 unique KBE tables were extracted. At least one clinical trial was specified in 273 (95.5%) of the KBEs (Table 1). Only 48 (16.8%) KBEs specified at least one extrapolation study, predominantly prevalent in the therapeutic areas of infectious diseases ($n = 9$, 23.7%), oncology ($n = 9$, 25.0%), endocrinology-gynaecology-fertility-metabolism ($n = 6$, 20.0%), immunology-rheumatology-transplantation ($n = 5$, 20.0%), pneumology-allergology ($n = 5$, 29.4%), and gastroenterology-hepatology ($n = 4$, 22.2%). All extrapolation studies included in the KBE tables in this analysis have been provided in Appendix 1.

Clinical trials specified in the KBEs typically had multiple aims, in which safety ($n = 254$, 88.8%), efficacy ($n = 192$, 67.1%) and pharmacokinetics ($n = 160$, 55.9%) were most frequently investigated per KBE table (Table 2). Extrapolation studies specified in the KBE tables typically aimed to extrapolate efficacy from a reference population ($n = 21$, 7.3%, Table 2). Population pharmacokinetic and/or pharmacodynamic modelling ($n = 20$) and physiology-based pharmacokinetic modelling ($n = 6$) were most frequently used methodologies in the extrapolation studies. The inclusion of extrapolation studies in PIPs has evolved over time: no extrapolation studies were included in PIPs published between 2008 and 2010, whereas 20% of the PIPs published between 2020 and 2022 included at least one extrapolation study (Figure 2A).

The youngest age group targeted in the KBE tables were newborn infants ($n = 78$, 27.3%), infants or toddlers ($n = 86$, 30.1%), children ($n = 100$, 34.9%) and adolescents ($n = 22$, 7.7%). Seventy-five (26.2%) KBEs aimed to investigate the full paediatric age range (0–18 years).

3.2 | Data extraction from the drug label

For 59 of the 286 unique KBE tables, a corresponding drug label could not be identified on the EMA website (Figure 1). For the remaining 227 unique KBE tables and associated therapeutic indications ($n = 238$), restrictions for use of the medicinal product in the paediatric population in the approved therapeutic indication were extracted from the drug label. No approval in the paediatric population was obtained in 43 (18.9%) therapeutic indications. Partial and full approval was obtained in 44 (19.4%) and 127 (55.9%) therapeutic indications, respectively. More than full approval was obtained in 24 (10.6%) therapeutic indications. The minimum age approved in the drug label covered newborn infants ($n = 60$, 25.2%), infants or toddlers ($n = 42$, 17.6%), children ($n = 69$, 29.0%) and adolescents ($n = 67$, 28.1%). Full approval of the paediatric age range was obtained in 24 (10.1%) therapeutic indications. In 15 (6.6%) therapeutic indications, use of the medicinal product in the paediatric population was restricted by specifying a minimum bodyweight (e.g., celsentri is indicated for patients weighing at least 10 kg [EMEA-C-000020-PIP01–07-M05]).

3.3 | Exposure-matching as support for the benefit/risk assessment

For the 238 therapeutic indications, where information on restrictions in the approved therapeutic indication were extracted from the drug

TABLE 1 Number of studies per unique key binding element table ($n = 286$).

Number	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 (4.6%)	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 (0.6%)	0 (0.0%)

TABLE 2 Aim of different studies specified in unique key binding element tables.

	Aim	*n* (%)
Quality	Development of a paediatric formulation	85 (29.7%)
	Evaluation of appropriateness of currently registered formulation	8 (2.8%)
	Other	5 (1.7%)
Non-clinical	Toxicity	52 (18.2%)
	Pharmacokinetics	11 (3.8%)
	Pharmacodynamics and/or pharmacokinetic/pharmacodynamic relationship	12 (4.2%)
	Biomarker	3 (1.0%)
	Carcinogenicity	1 (0.3%)
	Other	6 (2.1%)
Clinical	Pharmacokinetics	160 (55.9%)
	Pharmacodynamics	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%)
Extrapolation	Pharmacokinetics	8 (2.8%)
	Pharmacokinetic/pharmacodynamic relationship	1 (0.3%)
	Dose-finding	9 (3.1%)
	Extrapolation of efficacy	21 (7.3%)
	Other	23 (8.0%)

label, we found in the public assessment reports that 18 therapeutic indications did not apply for marketing authorization in the paediatric population. Additionally, no publicly available assessment reports could be identified for 33 therapeutic indications. This resulted in a total of 187 therapeutic indications, for which the benefit/risk assessment of paediatric marketing authorization applications could be evaluated. Additional sub-group analyses per therapeutic area, orphan disease status, and small *vs*. large molecules that were conducted for the 187 indications, for which a benefit/risk assessment could be evaluated, are presented in Table 3.

Exposure-matching was used to support the benefit/risk assessment for 74 (39.6%) of the paediatric marketing authorization applications (Table 4). The application of exposure-matching in support of the benefit/risk assessment has increased over time. Between 2008 and 2010, two exposure-matching studies (22.2%) were conducted, whereas 18 exposure-matching studies (41.9%) were performed between 2020 and 2021 (Figure 2B). The minimum age specified in the PIP and drug label was significantly higher for paediatric marketing authorization applications where the benefit/risk assessment was supported by exposure-matching (2.0 *vs*. 0.2 years, $P < .01$, and 2.0 *vs*. 0.5 years, $P < .01$, respectively). The targeted paediatric minimum age, specified in the PIP, was, however, comparable to the approved minimum age specified in the drug label for paediatric marketing authorization applications where the benefit/risk assessment was supported by exposure-matching (2.0 *vs*. 2.0 years, $P = .72$, Figure 3). This was, however, not the case for paediatric marketing authorization applications where the benefit/risk assessment was not supported by exposure-matching (0.2 years *vs*. 0.5 years,$P = .05$, Figure 3). Paediatric marketing authorization applications where the benefit/risk assessment was supported by exposure-matching were more likely to have a bodyweight cut-off specified in the indication (13.5% *vs*. 3.5%, $P = .01$).

The duration for obtaining PIP compliance was significantly longer for paediatric marketing authorization applications where the benefit/risk assessment was supported by exposure-matching (5.4 *vs*. 4.3 years, $P = .04$) and also typically required more modifications of the PIP (4 *vs*. 3, $P < .01$).

4 | DISCUSSION

Extrapolation based on exposure-matching appears to play a limited role in generating evidence to support paediatric marketing authorization applications as less than 20% of the planned drug development programmes explicitly specified an extrapolation study. In contrast, almost 40% of the paediatric marketing authorization applications used exposure-matching to support the benefit/risk assessment. Therefore, it can be concluded that the role of extrapolation based on exposure-matching in paediatric evidence generation is more pronounced than what can be expected based on the PIPs. The number of PIPs and marketing authorization applications incorporating extrapolation based on exposure-matching has progressively increased over time. Approved minimum age and bodyweight limits were more restrictive for marketing applications that used exposure-matching compared to those not supported by exposure-matching, which seems to suggest that exposure-matching is not a successful approach for obtaining marketing authorization. The targeted paediatric population did not significantly differ from the approved population for marketing authorization applications where the benefit/risk assessment was supported by extrapolation based on exposure-matching, whereas it did significantly differ for those not supported by exposure-matching. Therefore, extrapolation based on exposure-matching can be considered more successful for approval of the targeted population. On the other hand, duration of PIP completion was also significantly longer, and therefore seems less efficient than traditional approaches.

Manolis et al. reported that approximately 25% of PIPs specified quantitative methods in the drug development programme.[11] These quantitative methods were, however, also used for other purposes besides extrapolation, such as paediatric dosing regimen selection. This could imply that the role of extrapolation based on a quantitative comparison of exposure is limited in paediatric evidence generation. We found that less than 20% of the completed paediatric drug

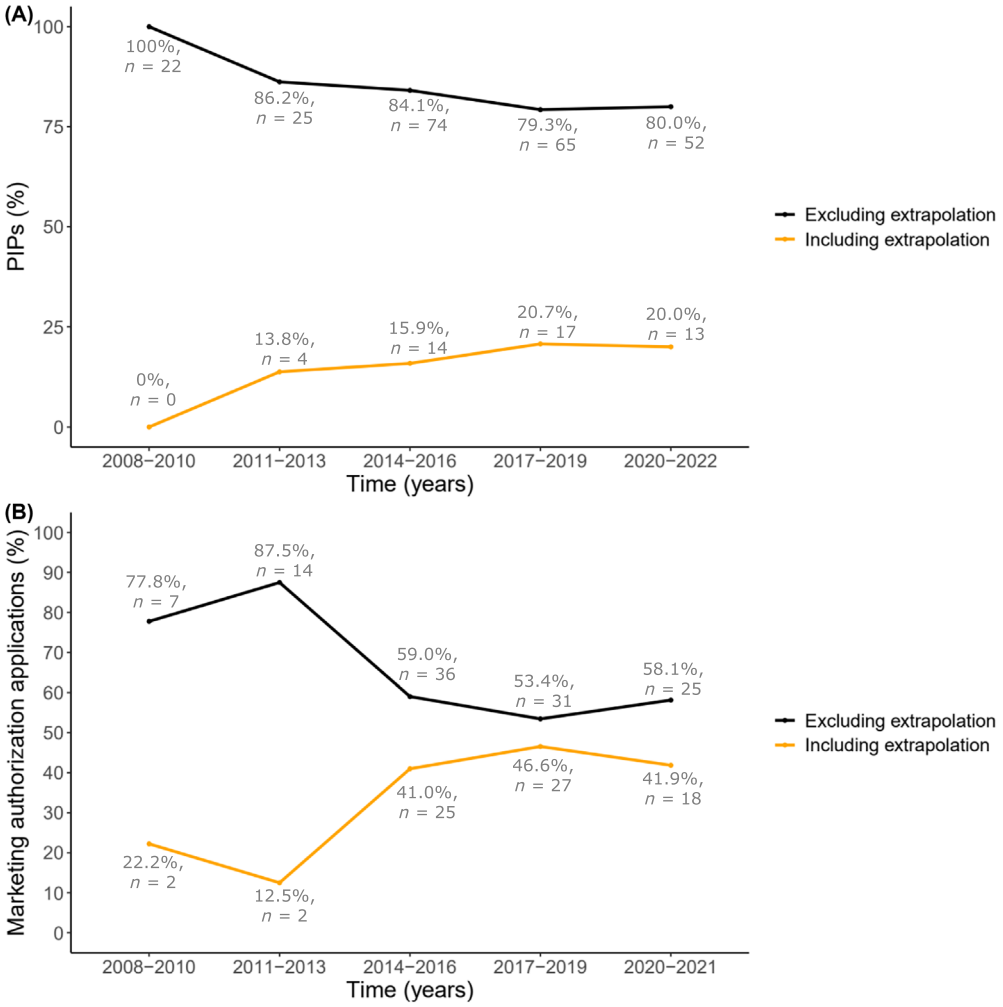

FIGURE 2 Percentage of PIPs (A) including or excluding an extrapolation study and percentage of marketing authorization applications (B) including or excluding extrapolation based on exposure-matching in the benefit/risk discussion.

development programmes explicitly specified an extrapolation study and extrapolation of efficacy was the main objective in only 7% of these studies. In contrast, approximately 56% of the planned drug development programmes specified at least one clinical trial that aimed to investigate the pharmacokinetic profile in the paediatric population, which could indicate that the role of extrapolation based on exposure-matching is more pronounced. Almost 40% of the paediatric marketing authorization applications used exposure-matching to support the benefit/risk assessment, which further supports this notion. It is considered difficult to extract the exact role of extrapolation from PIPs. Therefore, for future studies, we recommend a question-centric approach, which states how actual questions, attempted to be answered in the drug development programme, contribute to the benefit/risk assessment.[12] This allows academic researchers, paediatricians and other interested parties to challenge or further confirm the goals and assumptions of the drug development programme.

Ye et al. reported that approximately 64% of paediatric label changes between 2015 and 2021 reviewed by the FDA used some form of paediatric extrapolation, where 24% of the paediatric label changes relied fully on extrapolation.[13] In comparison, between 1998 and 2008, 82% of label changes reviewed by the FDA used some form of paediatric extrapolation, where 14% of the paediatric label changes relied fully on extrapolation.[13] Therefore, the overall use of extrapolation seems to be reduced in recent years. In contrast, our results indicate that extrapolation based on exposure-matching to support the benefit/risk discussion in the EU generally increased over time, where the benefit/risk discussion is supported in almost 40% of the therapeutic indications after 2013. This is in line with a shift towards more label changes based on a full extrapolation approach as observed for the FDA. Despite the overall lowering trend on the use of extrapolation in paediatric label changes in the US, Samuels et al.[14] showed that full extrapolation approaches increased from 34% to 51% between 1998 to 2008 and 2015 to 2020 in 15 therapeutic areas. The difference from the overall trend suggests that the role of extrapolation differs between therapeutic areas, which is also apparent in the subgroup analysis of this study. The assumptions of extrapolation in certain therapeutic areas could be more well established than in others and could indicate more research is needed towards the underlying assumptions of extrapolation to enhance the number of therapeutic indications eligible for an extrapolation approach. Recently, the FDA has reported results of such research where an alternative approach for extrapolation of efficacy based on similarity across compounds in schizophrenia and partial onset seizures was used.[15,16] These types of analyses strengthen our understanding of the potential

TABLE 3 Subgroup analyses per therapeutic area, orphan disease status, and small *vs.* large molecules for 187 indications for which the benefit/risk could be evaluated.

	No extrapolation (%)	Extrapolation (%)	Total studies (*n*)
Therapeutic area			
Infectious diseases	8 (25%)	24 (75%)	32
Haematology-Haemostaseology	20 (87.0%)	3 (13.0%)	23
Endocrinology-Gynaecology-Fertility-Metabolism	17 (77.3%)	5 (22.7%)	22
Oncology	11 (52.4%)	10 (47.6%)	21
Immunology-Rheumatology-Transplantation	11 (55%)	9 (45%)	20
Vaccines	15 (100%)	0 (0%)	15
Gastroenterology-Hepatology	6 (50%)	6 (50%)	12
Neurology	6 (54.5%)	5 (45.5%)	11
Other	3 (42.9%)	4 (57.1%)	7
Dermatology	3 (60%)	2 (40%)	5
Psychiatry	4 (80%)	1 (20%)	5
Pneumology-allergology	2 (50%)	2 (50%)	4
Cardiovascular diseases	1 (33.3%)	2 (66.7%)	3
Ophthalmology	3 (100%)	0 (0%)	3
Uro-nephrology	2 (66.7%)	1 (33.3%)	3
Neonatology-Paediatric Intensive Care	1 (100%)	0 (0%)	1
Orphan disease status			
No orphan disease	93 (58.9%)	65 (41.1%)	158
Orphan disease	20 (69.0%)	9 (31.0%)	29
Molecular size			
Small molecule (≤ 1000 g/mol)	46 (54.1%)	39 (45.9%)	85
Large molecule (> 1000 g/mol)	67 (65.7%)	35 (34.3%)	102

TABLE 4 Comparison between paediatric marketing applications that did and did not use extrapolation based on exposure-matching in support of the benefit/risk discussion of public assessment reports. Partially, fully, more than fully approved were defined as a lower, similar or higher approved minimum age as targeted in the PIP.

N	No extrapolation 113 (60.4%)	Extrapolation 74 (39.6%)	*P*-value
Duration of PIP compliance (years)	4.3 [1.5–6.9]	5.4 [3.3–7.5]	**0.04**
Number of PIP modifications (*n*)	3.0 [1.0–4.0]	4.0 [2.0–6.0]	**<0.01**
Minimum age in PIP (years)	0.2 [0.0–2.0]	2.0 [0.5–6.0]	**<0.01**
Minimum age in drug label (years)	0.5 [0.0–6.0]	2.0 [1.0–6.0]	**<0.01**
No approved paediatric indication (*n*)	5 (4.4%)	0 (0.0%)	0.07
Partially approved paediatric indication (*n*)	31 (27.4%)	12 (16.2%)	0.07
Fully approved paediatric indication (*n*)	67 (59.3%)	53 (71.6%)	0.08
More than fully approved paediatric indication (*n*)	10 (8.8%)	9 (12.2%)	0.46
Complete paediatric age range approved (*n*)	35 (31.0%)	13 (17.6%)	**0.04**
Bodyweight in indication (*n*)	4 (3.5%)	10 (13.5%)	**0.01**

Note: Results are expressed as *n* (%) or median [25th–75th percentile], significant *P*-values are expressed in bold.

for extrapolation of efficacy across compounds from the same class and mechanism of action. One could argue that these types of extrapolation are currently underused and this introduces another ethical aspect of potentially including larger paediatric populations than necessary in paediatric evidence generation.

Approximately 26% and 57% of the planned paediatric drug development programmes aimed to study the complete paediatric population or paediatric patients younger than 2 years, which aligns with previous observations that indicate that very young patients are often understudied.[17,18] Especially in newborn children, the PDCO is more likely to grant a waiver in the lower age groups (e.g., because there is no need for an indication, feasibility issues are expected or major safety risks are foreseen). Where extrapolation based on exposure-matching was used to support the benefit/risk assessment,

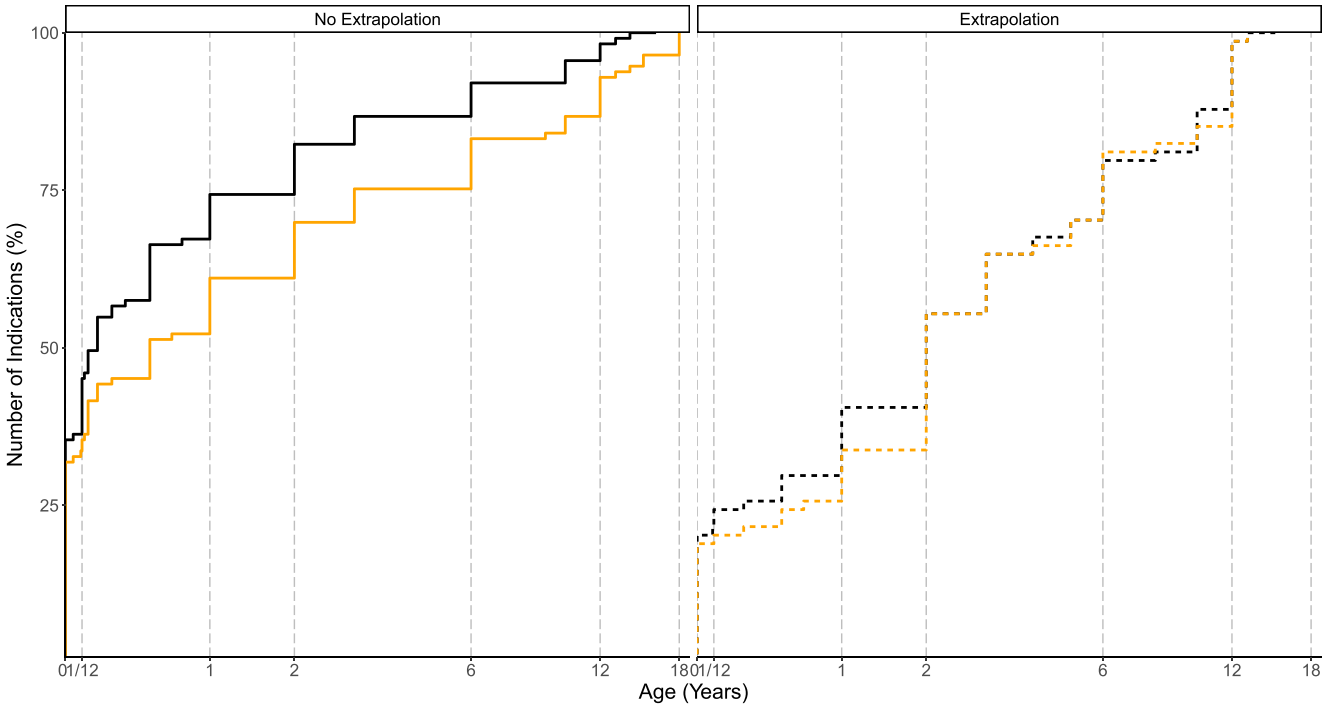

FIGURE 3 Cumulative number of indications *vs.* minimum age specified in PIP (black line) and in drug label (orange line) stratified by use of paediatric extrapolation based on exposure-matching.

the lower age groups were less likely to be included in the extrapolation study. This could imply that the PDCO is more reluctant to accept extrapolation based on exposure-matching in the paediatric population younger than 2 years. The youngest paediatric population is usually most distant from the reference (adult) population and thus prone to more uncertainties in the underlying assumptions of extrapolation. This could be the reason for the PDCO to be more reluctant to accept extrapolation in this population. With the introduction of the ICH M15 guideline, the weight of modelling and simulation analyses in the overall evidence generation is formalized, which is intended to facilitate a multidisciplinary understanding of model-informed drug development.[19] We hypothesize that this will increase the understanding and acceptance of model-based approaches, including exposure-matching, in paediatric drug development.

Ye et al. reported that the probability to obtain approval in the US of a new or expanded paediatric indication increased when paediatric extrapolation was used.[13] In the current study, the approved age range did not significantly differ from the targeted age range for paediatric marketing authorization applications that were supported by extrapolation based on exposure-matching, whereas the approved age range was significantly higher for those that were not. This supports the conclusions of the FDA that extrapolation based on exposure-matching is a more successful approach to generate evidence in the paediatric population.

Clinical trials required for an extrapolation approach are typically single-arm pharmacokinetic studies in a small population with a short follow-up. In contrast, clinical trials required for a traditional approach, in which efficacy and safety is demonstrated, are expected to be conducted in a large population with a long follow-up. Drug development programmes based on exposure-matching were therefore expected to be more efficient than traditional ones. In contrast, duration of PIP compliance was longer and PIPs were modified more often for marketing authorization applications where the benefit/risk assessment was supported by extrapolation based on exposure-matching. There is no clear explanation for this finding, but we speculate that clinical trials that are designed for exposure-matching may take longer to complete due to complexities in recruitment (fewer patients willing to participate to pharmacokinetic sample collection), trial design (staggered approach with a delay of inclusion of young patients) and lack of harmonized approach for demonstrating similarity in exposure. This will hopefully improve in the coming years with the new ICH E11A Guideline.[9]

Only publicly available information was used for the data collection and therefore there is a risk of publication bias, which is also apparent from the relatively high number of missing documents (i.e., drug labels and missing public assessment reports). The high number of missing documents can partially be explained by the focus on solely centralized paediatric marketing authorization applications and alternative routes for marketing authorization in the EU exist, such as only applying in a single European country. Additionally, drug companies are currently not obligated to apply for a paediatric indication after PIP compliance and, in such a case, no drug label is available. Furthermore, the structure of the European medicines regulatory network is very different to other regulatory agencies (e.g., FDA, PMDA). This adds uncertainty around the generalizability of our results to

other regions. At the same time, efforts to harmonize the methodologies and strategies for paediatric extrapolation have been ongoing since 2014, with the publication of the ICH concept paper on the revision of the E11 Guideline. Based on the similar results found in this paper and the FDA analysis, we hypothesize that despite structural differences in the regulatory networks across regions, it is not unlikely that a similar analysis based on submissions to other regulatory authorities may yield similar results. Lastly, we focused on paediatric extrapolation based on exposure-matching, but also other forms of paediatric extrapolation exist (such as leveraging of efficacy data from adult trials using Bayesian borrowing approaches). It is unknown how the results of this study translate to other paediatric extrapolation approaches.

In conclusion, paediatric marketing authorization applications where regulatory decision-making was supported by extrapolation based on exposure-matching were more successful in obtaining marketing approval in the targeted paediatric population compared to those not supported by extrapolation. However, despite the success, these paediatric marketing authorization applications are also less efficient.

AUTHOR CONTRIBUTIONS

C.W.M. Simons: data collection, analysis and interpretation of results, preparation of manuscript. L.C.H. Maton: analysis, interpretation of results, preparation of revised manuscript. M. van Dartel: study design, analysis and interpretation of results, preparation of manuscript. M. van den Heuvel: study design, analysis and interpretation of results, preparation of manuscript. L. den Otter: study design, analysis and interpretation of results, preparation of manuscript. C. Versantvoort: study design, analysis and interpretation of results, preparation of manuscript. P.J. Colin: study design, analysis and interpretation of results, preparation of manuscript. J.V. Koomen: study design, data collection, analysis and interpretation of results, preparation of manuscript.

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CONFLICT OF INTEREST STATEMENT

C.W.M. Simons, L.C.H. Maton, M. van Dartel, M. van den Heuvel, L. den Otter, C. Versantvoort and J.V. Koomen do not have any conflicts of interest to declare. Over the last 3 years, P.J. Colin's research group has been involved in contract research for PAION UK Ltd. (London, England) and Acacia Pharma Ltd. (Cambridge, England).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. CHMP. Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. EMEA/CHMP/EWP/147013/2004.
2. Kern SE. Challenges in conducting clinical trials in children: approaches for improving performance. *Expert Rev Clin Pharmacol*. 2009;2(6):609-617. doi:10.1586/ecp.09.40
3. Balan S, Hassali MAA, Mak VSL. Two decades of off-label prescribing in children: a literature review. *World J Pediatr*. 2018;14(6):528-540. doi:10.1007/s12519-018-0186-y
4. Allen HC, Garbe MC, Lees J, et al. Off-label medication use in children, more common than we think: a systematic review of the literature. *J Okla State Med Assoc*. 2018;111(8):776-783.
5. van der Zanden TM, Mooij MG, Vet NJ, et al. Benefit-risk assessment of off-label drug use in children: the Bravo framework. *Clin Pharmacol Ther*. 2021;110(4):952-965. doi:10.1002/cpt.2336
6. European Medicines Agency. Paediatric Regulation. https://www.ema.europa.eu/en/human-regulatory/overview/paediatric-medicines/paediatric-regulation. Accessed July 16, 2023.
7. European Medicines Agency. Paediatric Investigation Plans. https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans. Accessed July 16, 2023.
8. European Medicines Agency. Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018).
9. International Council for Harmonisation. Guideline E11A Paediatric Extrapolation. https://database.ich.org/sites/default/files/ICH_E11A_Document_Step2_Guideline_2022_0404_0.pdf. Accessed September 14, 2023.
10. European Medicines Agency. ICH Topic E11: clinical investigation of medicinal products in the paediatric population. https://www.ema.europa.eu/en/documents/scientific-guideline/e-11-clinical-investigation-medicinal-products-paediatric-population-step-5_en.pdf. Accessed January 8, 2025.
11. Manolis E, Osman TE, Herold R, et al. Role of modeling and simulation in pediatric investigation plans. *Paediatr Anaesth*. 2011;21(3):214-221. doi:10.1111/j.1460-9592.2011.03523.x
12. Musuamba FT, Cheung SYA, Colin P, et al. Moving toward a question-centric approach for regulatory decision making in the context of drug assessment. *Clin Pharmacol Ther*. 2023;114(1):41-50. doi:10.1002/cpt.2856
13. Ye J, Zhang V, Strimenopoulou F, et al. Recent use of pediatric extrapolation in pediatric drug development in US. *J Biopharm Stat*. 2023:1–15;33(6):681-695. doi:10.1080/10543406.2023.2170407
14. Samuels S, Park K, Bhatt-Mehta V, et al. Pediatric efficacy extrapolation in drug development submitted to the US Food and Drug Administration 2015-2020. *J Clin Pharmacol*. 2023;63(3):307-313. doi:10.1002/jcph.2160
15. Kalaria SN, Farchione TR, Uppoor R, Mehta M, Wang Y, Zhu H. Extrapolation of efficacy and dose selection in pediatrics: a case example of atypical antipsychotics in adolescents with schizophrenia and bipolar I disorder. *J Clin Pharmacol*. 2021;61(Suppl 1):S117-S124. doi:10.1002/jcph.1836
16. Mehrotra S, Bhattaram A, Krudys K, et al. Extrapolation of efficacy from adults to pediatric patients of drugs for treatment of partial onset seizures: a regulatory perspective. *Clin Pharmacol Ther*. 2022;112(4):853-863. doi:10.1002/cpt.2681
17. Hampson LV, Herold R, Posch M, Saperia J, Whitehead A. Bridging the gap: a review of dose investigations in paediatric investigation plans. *Br J Clin Pharmacol*. 2014;78(4):898-907. doi:10.1111/bcp.12402
18. Commission Staff Working Document Evaluation Joint Evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on Medicinal Products for

Paediatric Use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on Orphan Medicinal Products (2020). https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52020SC0163. Accessed September 14, 2023.
19. International Council for Harmonisation. Guideline M15 on general principles for model-informed drug development. https://database.ich.org/sites/default/files/ICH_M15_EWG_Step2_DraftGuideline_2024_1031.pdf. Accessed November 28, 2024.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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