# New Information on Old Medicinal Products: A Cross-Sectional Analysis of Guidance for Paediatric Use for Substances on the European Priority List of Off-Patent Medicinal Products

Ann-Katrine Birkelund Mogensen[1] · Helle Christiansen[1] · Marie Louise De Bruin[1,2] · Christine Erikstrup Hallgreen[1]

## Abstract

**Background** As part of the European Paediatric Regulation, the European Medicines Agency (former European Medicines Evaluation Agency) and the Paediatric Working Party (precursor for the Paediatric Committee) revised a priority list for studies on off-patent medicinal products in 2007 where a need for studies on paediatric medicinal products was emphasised.
**Objectives** We aimed to evaluate the status of guidance for paediatric use in the Summary of Product Characteristics for medicinal products on the priority list as well as the presence and status of Paediatric Investigation Plans for these medicinal products.
**Methods** We included active pharmaceutical ingredients on the priority list authorised through the centralised procedure and/or marketed in Denmark. The status of guidance for paediatric use (indication, posology and/or contraindication) was reviewed from the most recent Summary of Product Characteristics uploaded on the European Medicines Agency or the Danish Medicines Agency website as of November 2020. Information on Paediatric Investigation Plans status (Paediatric Committee opinion, completion and waivers granted) was retrieved from the European Medicines Agency website.
**Results** A total of 121 active pharmaceutical ingredients were included in this study. Seventy-one percent had guidance for paediatric use in the Summary of Product Characteristics for at least one paediatric subpopulation, more often concerning adolescents (70%) and children (70%) as compared with neonates (41%) and infants (49%). The guidance included a paediatric indication in 46% of the cases, but less often a contraindication (13%). Thirty-three active pharmaceutical ingredients had an agreed Paediatric Investigation Plan, six of these were completed.
**Conclusions** Most active pharmaceutical ingredients from the priority list had guidance for paediatric use in the Summary of Product Characteristics. However, there is still an unmet need in relation to guidance for use for the youngest paediatric subpopulation.

## 1 Introduction

Up to 70% of medicines used to treat the paediatric population, aged 0–18 years, are prescribed off-label and for premature newborns, neonates, and infants the frequency of off-label prescription is up to 90% [1–4]. The need to prescribe off-label is often owing to the lack of therapeutic options and the absence of data supporting the use of medicines within the paediatric population [5]. Treatment options would be extremely limited and paediatric patient safety jeopardised if clinicians could only prescribe medicines licensed for the paediatric population [6]. Therefore, prescription for children is often off-label and based on information from clinical adult studies, clinical guidelines, scientific literature or the prescribing physicians' anecdotal evidence. Several studies have indicated that off-label prescription in children may increase the risk of adverse drug reactions [7–9], which may be because of physiological differences between the paediatric and adult populations in respect to pharmacokinetics and pharmacodynamics [10]. The paediatric population may metabolise

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✉ Christine Erikstrup Hallgreen
christine.hallgreen@sund.ku.dk

1 Copenhagen Centre for Regulatory Science, Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

2 Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

certain medicines differently compared to adults resulting in a lack of treatment efficacy and/or adverse drug reactions [11]. For example, the medicinal product theophylline is metabolised by a different pathway in children than in adults causing the production of caffeine. This needs to be monitored closely to prevent adverse drug reactions in neonates [12].

As a response to the lack of evidence and approval of medicines for children, the European Parliament and European Council in 2006 agreed on the European Paediatric Regulation (EPR), which came into force in 2007 [13]. The regulation was set in place to stimulate the development of paediatric medicine and provide more information on the use of medicine in children. To achieve this, regulatory requirements and incentives/rewards for the development of medicinal products for use in children were established [14–16]. Most notably, the EPR introduced a new type of marketing authorisation, namely the Paediatric Use Marketing Authorisation (PUMA) [Articles 30 and 31] [17]. The PUMA concept focusses on stimulating paediatric research in existing off-patent medicinal products and helping the transformation of known off-label uses into authorised use, i.e. to provide better and safer drug formulations for children in different subpopulations. Although a PUMA provides the manufacturer with a 10-year period of marketing protection, very few PUMAs have been granted [17, 18]. To further stimulate paediatric drug development for off-patent medicinal products, Article 40 of the EPR allocated funding for research to support PUMAs [17]. In this context, a priority list for studies on off-patent medicinal products (from here on referred to as the priority list) was established to ensure that funding through the Seventh Framework Programme from 2007 to 2013 was dedicated to research on medicinal products with the highest need in the paediatric population not covered by a patent or a supplementary protection certificate [19]. The priority list was initially developed in 2004 by the European Medicines Agency (EMA) [former European Medicines Evaluation Agency] upon request from the European Commission. The EMA developed the priority list in collaboration with the Committee for Medicinal Products for Human Use Paediatric Expert Group, which consulted with European specialists and experts in paediatrics. The list has subsequently been updated several times. In 2007, the Paediatric Working Party (precursor for the Paediatric Committee [PDCO]) revised and adopted the priority list. The latest update was in 2013 in preparation for the Horizon 2020 Programme of the European Commission.

Results from previous studies on the EPR indicate that it has had the greatest impact on new medicinal products but only limited effect on medicinal products used off-label in the paediatric population and therapeutic areas only affecting the paediatric population [20–23]. In addition, the literature indicates that the PUMA incentive has not been of sufficient interest to the pharmaceutical industry because of limited economic returns [4, 24].

To our knowledge, the impact of the establishment of the priority list on the available guidance for paediatric use in the Summary of Product Characteristics (SmPCs) has not yet been evaluated. Therefore, the objective of this study was to give an up-to-date overview of the guidance for paediatric use in these off-patent products labelled as having a high need for guidance for paediatric use. In addition, this study investigated the presence and status of Paediatric Investigation Plans (PIPs) for these medicinal products.

## 2 Methods

### 2.1 Study Design

This cross-sectional study included all medicinal products containing an active pharmaceutical ingredient (API) listed on the priority list of off-patent medicinal products. The analysis included the guidance for paediatric use in the most recent SmPC and the status of PIPs as of November 2020. All versions of the priority list of off-patent medicinal products published between 2004 and 2013 (where the latest version was published), in total eight, were retrieved. The newest version of the priority list was retrieved from the EMA website [19] and the older versions were kindly provided by Wimmer et al. [21].

### 2.2 Data Collection

All APIs or API fixed combinations listed on at least one of the versions of the priority lists were identified. Listings were excluded if stated as a drug class and/or a group of therapeutic agents (e.g. angiotensin-converting enzyme inhibitors or intranasal corticosteroids) or otherwise not specified with a specific API(s). Furthermore, APIs were excluded if no effective SmPC was available for the API in either the European Assessment Report on the EMA website [25] or the Danish Medicines Agency website (produktresume.dk) [26]. Summary of Product Characteristics from the Danish Medicines Agency website was included to obtain information on APIs from the older priority lists that have not been approved through the centralised procedure. Details on product approval (approval through the centralised or national procedure) was obtained.

All APIs identified in the study sample were classified according to the therapeutic area as defined by the World Health Organization Anatomical Therapeutic Chemical codes. First appearance on the priority list and product age defined as the earliest European Union reference date (time since first granted a marketing authorisation for a specific API) were recorded [27, 28]. In addition, information of

whether an API has been granted a PUMA was recorded based on reports to the European Commission [29–33].

The latest updated effective SmPC available from the EMA website or produktresume.dk for all medicinal products for a given API was retrieved. Because one API can be marketed with different strengths, formulations and/or administration routes, it can have multiple SmPCs. If an API had several SmPCs with the same strength, formulation and/or administration route, only the most recently updated SmPC was included for assessment. This method resulted in a 'collection of SmPCs' for each API representing the current guidance for paediatric use for the specific API or API fixed combinations.

Summary of Product Characteristics was evaluated for details on guidance for paediatric use for each paediatric subpopulation using definitions from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline: age 0–27 days were defined as neonates, age 28 days to 23 months infants, age 2–11 years children and age 12–18 years adolescents [16, 34]. Guidance for paediatric use was classified as APIs having an approved paediatric indication (Sect. 4.1 of the SmPC) and/or paediatric posology information (Sect. 4.2 of the SmPC) and/or a paediatric contraindication (SmPC Sect. 4.3) for one or more paediatric subpopulations.

The most recent PDCO opinion was retrieved for each API from the EMA table for all opinions and decisions on PIPs downloaded from the EMA website [35]. For all APIs for which a PDCO opinion was published, we recorded the date for which this opinion was confirmed by the EMA, as well as any date of modifications to this opinion. For the most recent version of the PIP, we collected the planned completion date, granted waivers for each paediatric subpopulation or agreement of a PIP. When possible, PIP compliance status (completed/not) and PIP compliance date were collected. When a full waiver is granted, it only relates to the condition(s) for which the PIP is applied for.

All data were extracted and interpreted by one researcher (AKM). A second researcher (CEH) was consulted in cases of uncertainties. In addition, a random sample of APIs from the study sample was reviewed by a third researcher (HC) to check for any discrepancies. A spreadsheet of the raw data can be viewed in the Electronic Supplementary Material (ESM).

## 2.3 Data Analysis

The year for the APIs first appearance on the priority list as well as therapeutic areas for APIs was analysed with simple descriptive statistical procedures. Median time and interquartile range (IQR) for product age was calculated (years between marketing approval and the time of analysis, 2020).

The total number of APIs and number of APIs with guidance for paediatric use for at least one paediatric subpopulation in the SmPC were quantified and presented as absolute numbers and percentages relative to the total numbers of APIs and relative to the total number of APIs with guidance for paediatric use. Furthermore, a descriptive analysis was used to evaluate the PIP information, which included median time and IQR for PIP timing. All analyses were performed at the API level, merging the information from multiple SmPCs or PIPs within the respective collections per API or API fixed combination.

A chi-square test was performed to test whether there was a difference between the four paediatric subpopulations and those having guidance for paediatric use in the SmPC. A $p$-value of <0.05 was considered statistically significant. If this test was statistically significant, a chi-square test between each paediatric subpopulation was conducted to identify which subpopulation(s) differ from the others. Bonferroni correction was used to take account of multiple comparisons. All data analyses were performed using IBM® SPSS® Statistics Version 27 [36].

## 3 Results

A total of 533 medicinal products and/or drug classes were listed on the priority lists of off-patent medicinal products from 2004 and until the latest updated version in 2013. Of these, 121 APIs were eligible for this study (Fig. 1).

### 3.1 Study Sample Characteristics

Thirty-eight percent ($n = 46$) of the APIs in the study sample were included on the first priority list in 2004 and a further 61 APIs (50%) were added in the following 6 years (before 2010). From 2011 to 2013, 14 APIs were added to the list (no APIs were added in 2010) [Table S2 of the ESM]. Seventy-six percent ($n = 82$) of the APIs were later removed on the following published priority lists, 22 of these reappeared on the list later on (Table S3 of the ESM). The median product age for the APIs at the end of the follow-up (years between first marketing approval and the time of analysis, 2020) was 41 years (IQR 29–54 years). Eighty percent ($n = 97$) of the APIs in the study sample were approved nationally, 2% ($n = 2$) were approved through the centralised procedure and 18% ($n = 22$) were approved both through the national and centralised procedures.

The 121 APIs referred to 137 unique Anatomical Therapeutic Chemical codes. The APIs on the priority list represented the therapeutic areas of antineoplastic and immunomodulating agents in 26% of the cases, and the cardiovascular system in 23% of the cases (Table 1). Of APIs with guidance for use ($n = 86$), in at least one paediatric

**Fig. 1** Flowchart of study
cohort and exclusion criteria.
*Therapeutic group/nonspecific
active pharmaceutical ingre-
dient (APIs) were excluded
(Table S1 of the ESM). *SmPC*
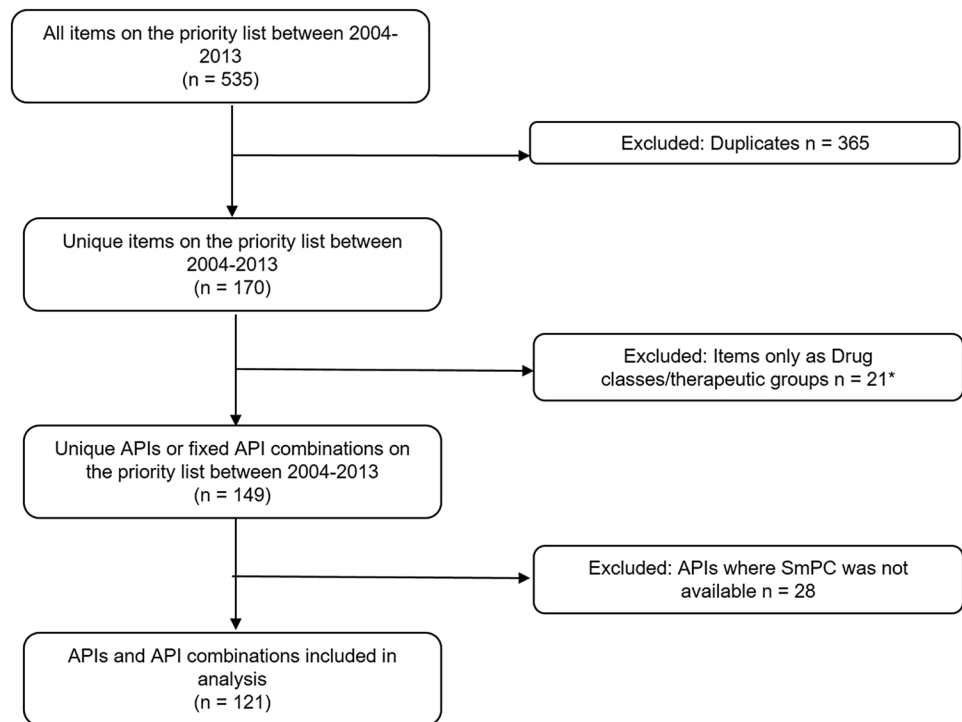Summary of Product Charac-
teristics



Flowchart:
- All items on the priority list between 2004-2013 (n = 535)
  - Excluded: Duplicates n = 365
- Unique items on the priority list between 2004-2013 (n = 170)
  - Excluded: Items only as Drug classes/therapeutic groups n = 21*
- Unique APIs or fixed API combinations on the priority list between 2004-2013 (n = 149)
  - Excluded: APIs where SmPC was not available n = 28
- APIs and API combinations included in analysis (n = 121)

**Table 1** Therapeutic areas for the APIs in the study sample and for APIs that had guidance for paediatric use for at least one paediatric subpopu-
lation in the SmPC

| ATC, first level | APIs $N^a$ (%$^b$) | APIs with guidance for paediatric use $N$ (%$^b$) |
|---|---|---|
| Total number of APIs | 121 | 86 |
| Antineoplastic and immunomodulating agents, L | 31 (26%) | 18 (21%) |
| Cardiovascular system, C | 28 (23%) | 15 (17%) |
| Nervous system, N | 22 (18%) | 18 (21%) |
| Anti-infective for systemic use, J | 12 (10%) | 11 (13%) |
| Alimentary tract and metabolism, A | 12 (10%) | 10 (12%) |
| Musculoskeletal system, M | 6 (5%) | 4 (5%) |
| Sensory organs, S | 6 (5%) | 4 (5%) |
| Systemic hormonal preparations, excluding sex hormones and insulins, H | 5 (4%) | 5 (6%) |
| Respiratory system, R | 4 (3%) | 4 (5%) |
| Dermatological, D | 4 (3%) | 2 (2%) |
| Blood and blood forming organs, B | 3 (2%) | 2 (2%) |
| Genito-urinary systems and sex hormones, G | 2 (2%) | 0 (0%) |
| Antiparasitic products, insecticides and repellents, P | 1 (1%) | 1 (1%) |
| Various, V | 1 (1%) | 0 (0%) |

*API* active pharmaceutical ingredient, *ATC* Anatomical Therapeutic Chemical Classification, *SmPC* Summary of Product Characteristics

[a]The 121 APIs referred to 137 unique ATC codes, as 11 APIs were connected to more than one ATC code in the SmPCs

[b]Percentages calculated from the total number of APIs. It does not sum up to 100%

subpopulation, the therapeutic area frequently represented were antineoplastic and immunomodulating agents (21%) and agents for the nervous system (21%) (Table 1).

## 3.2 Guidance for Paediatric Use

Overall, 71% ($n = 86$) of the 121 APIs had guidance for paediatric use in at least one paediatric subpopulation in the latest updated SmPC. A significant difference in guidance for paediatric use was observed between paediatric subpopulations ($p < 0.0001$). It was more common for children (70%) and adolescents (70%) to have guidance for paediatric use compared with neonates (41%) and infants (49%) ($p < 0.0001$, Table 2).

Forty-six percent ($n = 56$) of all 121 APIs had a paediatric indication in at least one paediatric subpopulation, often covering adolescents ($n = 55$) and children ($n = 52$). Sixteen (13%) of the 121 APIs had a contraindication for at least one paediatric subpopulation, all including neonates (Table 2). Twenty-four (20%) APIs had paediatric posology

information in the SmPC without a paediatric indication or contraindication. This was most frequent in children ($n = 27$, 22%) and adolescents ($n = 25$, 21%).

## 3.3 Paediatric Investigation Plan

Thirty-nine (32%) of the APIs had a PDCO opinion on paediatric development. Of these, seven were granted a full waiver and 32 had an agreed PIP, of which six had a positive compliance check at the end of the follow-up (Table 3). Of the six positive compliance checks, three PUMAs had been granted for medicinal products containing the APIs: hydrocortisone, midazolam and propranolol. The median time between an agreed PIP and a positive compliance check was 2.9 years (IQR 0.8–4.3 years). Of the seven APIs that had been granted a full waiver, three of them were for another condition than stated in the priority list and four were for the condition stated in the priority list but waived on one of the following grounds: "The specific medicinal product does not represent a significant therapeutic benefit over existing

**Table 2** Overview of frequencies of paediatric indication, contraindication, paediatric posology information or no guidance for paediatric use in total and within each paediatric subpopulation. All calculations were based on percentage of total APIs in the study sample ($n = 121$)

| | One or more paediatric subpopulation(s) | Neonates (aged 0–27 days) | Infants (aged 28 days to 23 months) | Children (aged 2–11 years) | Adolescents (aged 12–18 years) |
|---|---|---|---|---|---|
| | $N$ (%) | $N$ (%) | $N$ (%) | $N$ (%) | $N$ (%) |
| Guidance for use | 86 (71%) | 49[a] (41%) | 59[a] (49%) | 85[a] (70%) | 85[a] (70%) |
| Indication | 56 (46%) | 20 (17%) | 31 (26%) | 52 (43%) | 55 (46%) |
| Contraindication | 16[b] (13%) | 16 (13%) | 14 (12%) | 9 (7%) | 8 (7%) |
| Only posology information | 24 (20%) | 16 (13%) | 20 (17%) | 27 (22%) | 25 (21%) |
| No guidance for use | 35 (29%) | 72 (60%) | 62 (51%) | 36 (30%) | 36 (30%) |

*API* active pharmaceutical ingredient

[a]Chi-square test of hypothesis for guidance for paediatric use. Result: neonates vs children/adolescents ($X^2$ (1, $N = 242$) = 21, $p < 0.0001$), infants vs children/adolescents ($X^2$ (1, $N = 242$) = 12, $p = 0.001$), neonates vs infants ($X^2$ (1, $N = 242$) = 2, $p = 0.196$) and children vs adolescents ($X^2$ (1, $N = 242$) = 0, $p = 1.000$)

[b]Some APIs had a paediatric indication for one paediatric subpopulation and a paediatric contraindication for another subpopulation at the same time

**Table 3** Characteristics of PIP status for the 39 APIs in the study sample having a PDCO opinion on paediatric development. All calculations were based on percentage of total PDCO opinions ($n = 39$)

| | $N$ (%) | Median time (years) |
|---|---|---|
| PIPs completed | 6 (15%) | |
| Time between agreed PIP and positive compliance check | | 2.9 (IQR 0.8–4.3) |
| PIPs not completed (expected completion later than 2020) | 6 (15%) | |
| PIPs not completed | 20 (51%) | |
| Time exceeded expected completion date | | 4.3 (IQR 2.9–5.5) |
| PIPs waived from studies within all paediatric subpopulations | 7 (18%) | |

*API* active pharmaceutical ingredient, *IQR* interquartile range, *PDCO* Paediatric Committee at the European Medicines Agency, *PIP* Paediatric Investigation Plan

treatments", "the specific medicinal product is likely to be unsafe" or "the specific medicinal product does not represent a significant therapeutic benefit over existing treatments".

Twenty-one of the PIPs (20/32) had exceeded the expected date of completion for the PIP without having a positive compliance check at the time of this study. The median time for exceeding the expected completion date was 4.3 years (IQR 2.8–5.5 years) (Table 3).

Out of the 39 APIs with a PDCO opinion, 24 had guidance for paediatric use in the SmPC for at least one paediatric subpopulation, but not necessarily for the condition(s) stated in the priority list. For the six APIs that had a positive compliance check, all had guidance for paediatric use in the SmPC. All seven APIs granted a full waiver had guidance for paediatric use for at least one paediatric subpopulation.

## 4 Discussion

This study demonstrates that 7 years after the latest update of the priority list of off-patent medicinal products, most of the APIs on the list (71%) have guidance for paediatric use in the SmPC for at least one paediatric subpopulation. Guidance for paediatric use is significantly more frequent for adolescents (70%) and children (70%) compared with neonates (41%) and infants (49%). For almost all (12/14) therapeutic areas on the priority list, we found at least one API with guidance for paediatric use. This contrasts with a previous study by Pandolfini and Bonati, where a lack of overlap between therapeutic need and research in the paediatric population was noted. In their study, only four of the 25 conditions on the priority list of off-patent medicinal products were investigated in clinical trials at the time [37]. Results from our study therefore indicate increased guidance for paediatric use in the SmPCs compared with the time right after the entry of the EPR. Guidance for paediatric use can of course also stem from other sources than the SmPC such as the scientific literature or experience from well-established clinical use [6].

About half (46%) of the APIs on the priority list have a paediatric indication, of which adolescents was the paediatric subpopulation that most frequently had an indication. Only around one-fifth of the APIs have an indication for neonates and one-fourth for infants, possibly reflecting the challenges of including these subpopulations in clinical drug development [38–40]. Only a limited number (13%) of the APIs have a paediatric contraindication, most frequently for the youngest subpopulations, and all contraindications included the neonatal subpopulation. This was also observed in a study by Wimmer et al., where neonates was the paediatric subpopulation that most frequently had a contraindication or warnings in the SmPCs [41]. Neonates have a high priority when it comes to guidance for use; however, this

population is rarely studied, and medicines are still used off-label with potentially high risks [42]. Our findings suggests that 16 years after the priority list was adopted, guidance for use in the SmPC is still lagging for neonates. A study by Turner et al. concluded that neonatal markets are relatively small and well-known off-patent medicinal products are widely used. They suggest that this leads to insufficient incentives for the pharmaceutical industry to develop and conduct research within this specific paediatric subpopulation even after the initiatives provided with the EPR [43]. It is, however, also important to note that neonates represent a small subpopulation, from 0 to 27 days, compared with the others that include several years in the subpopulation, for example children (aged 2–11 years). Other important factors to take into consideration in respect to neonates are the logistical and ethical challenges in performing clinical trials and the lack of incentives for clinical or neontologists/paediatricians to conduct clinical trials within this subpopulation. Nonetheless, there is still a high unmet need for guidance for paediatric use in relation to this subpopulation [38–40].

Less than one-third (26%, 32/121) of the included APIs in our study have an agreed PIP, and only six of those were completed. Nevertheless, it is an improvement compared with the study by Wimmer et al., which reported even lower levels of PIPs (11%) for APIs on the priority list [21]. In addition, a study by Haslund-Krog et al. also observed that the EPR has failed in decreasing off-label use [23]. Of the 100 most commonly used drug substances for the paediatric population in Denmark, 13 were being used off-label because of a lack of paediatric indication. Five of these had a PIP and/or a waiver; however, none of the PIPs was completed at the time of the study [23].

The purpose of the priority list is to support the assessments of applications for funding through the European Union Framework Programmes and thereby ensuring that funds are directed into off-patent medicinal products with the highest need in the paediatric population to foster PUMAs [19]. Alongside the European Union programme, there are other funding schemes available for clinical research. In total, six PUMAs have been granted since the entry of the EPR at the time of this study (from 2007 to 2020) [29–33]. This is an increase compared with a study by Wimmer et al. who reported that no PIPs in relation to the priority list had led to a PUMA at the time of their study [21]. Currently, the PUMA incentive may not be profitable enough for the pharmaceutical industry, and they might instead focus their efforts on research and development within more profitable segments [24].

An important point of view rarely represented in the literature is that off-label medicinal products used in the paediatric population are necessary for important and even lifesaving purposes [6, 44]. Off-label use is often viewed as off-evidence from a regulatory perspective. However, this is

not always the case in clinical practice, where treatment of the paediatric population is often based on evidence from clinical guidelines [6].

A study by van der Zanden et al. proposed an alternative to the traditional regulatory pathway to ensure that the paediatric population is treated in the best possible way using the most current evidence available from all accessible sources [6]. They introduced a new initiative in the Netherlands aiming at encouraging uniformity in paediatric prescribing habits through a paediatric treatment guideline based on the best available evidence from registration data, investigator-initiated research, professional guidelines, clinical experience and consensus. This Dutch Paediatric Formulary provided insights into the overall evidence available and not just the evidence provided in the SmPCs [6]. In light of the limited economic incentive for the pharmaceutical industry to conduct research on off-patent medicinal products, initiatives such as the Dutch Paediatric Formulary [45] may be another and more feasible method to help paediatric prescribers in daily practice obtain an overview of the necessary information needed for treating the paediatric population in the best possible way. A similar initiative has been initiated in Denmark with the purpose of establishing a national centre that can provide higher quality evidence on the use of safe medicines for the paediatric population as a reaction to the lack of collected national clinical guidelines [46, 47]. While these initiatives may provide support for physicians in their clinical decision making, the national formularies cannot replace legally adding an indication to a medicinal product.

### 4.1 Strengths and Limitations

Results from this study should be interpreted in relation to its strengths and limitations. The study sample was limited to the priority list of off-patent medicinal products and not the wider list of paediatric needs compiled by the EMA. The current literature indicates that the EPR has had the greatest impact on new medicinal products [22]. Even though only a few PUMAs have been granted, this does not necessarily mean that no guidance for paediatric use has become available for these off-label medicinal products. This made it interesting to review the status of guidance for paediatric use for these off-patent medicinal products that are categorised by the EMA as medicinal products with the highest need in the paediatric population.

We systematically collected information from SmPCs of APIs on the priority lists approved through the centralised procedure for the whole of Europe or marketed in Denmark. Active pharmaceutical ingredients on the priority list that were either approved through national pathways or not marketed in Denmark were excluded from this study. We did not observe any pattern in the therapeutic areas of excluded

APIs (Fig. S1 of the ESM). The analysis in this study reported the guidance for paediatric use for an API, not per medicinal product and independent of whether it was for the condition(s) stated in the priority list. Hence, the guidance for paediatric use reported here may not be reflected in all SmPCs for a given API.

Paediatric subpopulations represented in the SmPCs did not always follow the same age range as defined by ICH (neonates, infants, children and adolescents). If only part of an ICH-defined subpopulation was referred to in the SmPC, this was recorded as guidance for the entire paediatric population. Some SmPCs did not provide age ranges but rather referred to for example, 'children' or 'paediatric population'. In these instances, the information was considered to relate to all four ICH-defined subpopulations. This may have resulted in an overestimation of which paediatric subpopulation has guidance for use in the SmPCs. Furthermore, we did not investigate whether the APIs from the priority list were off-patent or whether medicinal products including the APIs from the list were products frequently used in the paediatric population today, nor did we evaluate the level of guidance for paediatric use for the APIs when entering the priority list.

## 5 Conclusions

This study demonstrates that most APIs from the priority list of off-patent medicinal products with a high need for the paediatric population have guidance for paediatric use in the SmPC, but some unmet needs still remain, particularly for the neonatal paediatric subpopulation.

patient organisations (Rare Diseases Denmark). The centre is purely devoted to the scientific aspects within the regulatory field and with a patient-oriented focus whilst the research is not a company-specific product or directly company related. Helle Christiansen is a PhD student at CORS. Her project is funded by a grant from Lundbeck A/S to the CORS. At the time of the study, Marie Louise De Bruin was an employee at CORS. Currently, she is employed by Utrecht University to conduct research under the umbrella of the Utrecht Centre for Pharmaceutical Policy and Regulation. This centre receives no direct funding or donations from private parties, including the pharma industry. Research funding from public-private partnerships, for example, IMI, The Escher Project (http://escher.lygature.org/), is accepted under the condition that no company-specific study is conducted. The centre has received unrestricted research funding from public sources, for example, World Health Organization, Netherlands Organisation for Health Research and Development, the Dutch National Health Care Institute, European Commission Horizon 2020, the Dutch Medicines Evaluation Board and the Dutch Ministry of Health. Ann-Katrine Birkelund Mogensen was during the study period from August 2020 to January 2021 a master thesis student at the University of Copenhagen at CORS. During this period, AKM worked part-time as a student assistant in the generic pharmaceutical company Sandoz A/S. After graduation in January 2021, and currently, AKM is working at Sandoz A/S. Sandoz A/S was not involved in any aspect of this study.

**Ethics approval** Not applicable.

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Availability of data and material** Data collected for the purpose of this study are included in this published article as supplementary information.

**Code availability** Not applicable.

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