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Does the EU's Paediatric Regulation work for new medicines for children in Denmark, Finland, Norway and Sweden? A cross-sectional study

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ABSTRACT

Objective The aim of this study was to assess the marketing status of the new paediatric medicinal products listed in the 10-year report as initially authorised between 2007 and 2016, reflecting the product availability in four Nordic countries.

Design This is a cross-sectional study.

Setting Analysis of the national medicine agency's databases in Denmark, Finland, Norway and Sweden.

Data source New medicinal products with paediatric indications and new paediatric formulations listed in the Annex of European Medicines Agency's EU Paediatric Regulation 10-year report.

Data analysis The products were classified according to national marketing status between January 2019 and March 2019, whether a product was authorised and whether the product was marketed.

Main outcome measures The percentages of the new medicinal products with paediatric indications and new paediatric formulations having a valid marketing authorisation and being marketed, both in terms of the sums of all countries and separately for each country.

Results Across the four countries, 21%–32% (16/76–24/76) of the new medicinal products were not marketed. Of the new formulations relevant to children, 29%–50% (16/56–28/56) were not marketed, and a significant proportion of these products had never been marketed.

Conclusions This study reflects the reality of the implementation of the Paediatric Regulation. The results show that several new paediatric medicines and new formulations are not marketed. This affects the product availability. Similar data from other countries are needed to evaluate the overall European status to find remedies to current situation and increase the availability of the medicines for children.

What is known about the subject?

- The aim of the Paediatric Regulation (EU 1901/2006) is to improve the health of children by facilitating the development and availability of paediatric medicines.
- In 2017, the European Medicines Agency published a 10-year report, and concluded that a significant number of new medicines for children have been authorised.
- Marketing authorisation is no guarantee that a new medicine is available for all patients, as the accessibility to medicines varies across countries.

What this study adds?

- 21%–32% (16/76–24/76) of the new medicines initially authorised for children between 2007 and 2016 were not marketed across the four Nordic countries.
- 29%–50% (16/56–28/56) of the new paediatric formulations were not marketed and a significant proportion had never been marketed.
- Despite the intentions of the EU's Paediatric Regulation, medicines targeted at children are not all marketed, risking limitations in availability and accessibility for patients.

INTRODUCTION

The benefit of new therapies has not reached children to the same extent as the adult population throughout the history of drug development. Children still lack medicines across many therapeutic areas and all age groups, as well as age-appropriate formulations, adequate dosing and administration instructions in the product labelling. Increased knowledge and revised attitudes have prompted practical actions to improve the situation in the form of new legislation. In Europe, the Paediatric Regulation (EU 1901/2006 and 1902/2006) was implemented on 26 January 2007.[1]

The aim of the Paediatric Regulation is to improve the health of children in Europe by facilitating the development and availability of medicines for children. To achieve this, the regulation includes a system of obligations, rewards and incentives for the pharmaceutical industry. It applies to all new medicines aiming for a Marketing Authorisation (MA)

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in Europe, as well as to authorised, patent-protected medicines, when these are developed with new indications, routes of administration or pharmaceutical forms for children. In these cases, the company must make a development plan for the product (paediatric investigation plan, PIP), which must be agreed on by the European Medicines Agency's (EMA) Paediatric Committee.[2] For older off-patent products, the regulation offers a new Paediatric-Use Marketing Authorisation status for the new paediatric-only products.

In the European Commission's (EC) 10-year report in 2017 on the implementation of the Paediatric Regulation,[3] and the background report from EMA,[4] a clear positive effect was demonstrated in several areas. One of these was the number of authorised new medicines for the period between 2007 and 2016. The data indicated that the regulation has facilitated paediatric medicine development, resulting in new products with initial paediatric indication, extensions of previously authorised products to children and new formulations or strengths suitable for children. All these are listed in the Annex (Chapter 1) to the EMA's 10-year report.[4]

Safety, efficacy and quality data are required for all medicines seeking MA. After MA, the product can be placed on the market, allowing patient's access to the new medicine through official commercial channels. However, the choice to place an authorised product on the market in a specific country is the decision of the MA holder (ie, the company). The product may be marketed only in selected countries, resulting in variations in 'real-world access' to medicines.

Several recent reports have focused on the various developments and achievements that have followed the Paediatric Regulation,[5–11] but to the best of our knowledge, no studies have reported on the actual country-specific marketing status after the Paediatric Regulation implementation. The aim of this study was to assess the current marketing status (having MA and being marketed) of the new medicinal products and new formulations listed in the Annex of the EMA's 10-year report on each of the four countries.

MATERIALS AND METHODS

Research ethics approval

No patients nor voluntary participants were involved in this study, so no ethics review was needed.

Data collection

The study target was to investigate the marketing status of new medicines for children in four Nordic countries during the predefined period between January 2019 and March 2019. The term 'marketing status' refers to whether a product was authorised (having a valid MA) and whether the product was marketed, during the time of the study period, based on the regulatory classification of the products.

Data source

The products studied were those listed as having been authorised in Europe between 2007 and 2016 according to the Annex of the EMA's 10-year report to the EC.[4] This included (a) new medicinal products authorised with a paediatric indication at the time of the initial MA and (b) new formulations (ie, new pharmaceutical forms and strengths) relevant for children as listed in the Annex tables 1, 3 and 6. Information on the source data for this study is given in table 1.

Data were collected from the national Medicine Authority databases: Denmark (DK): KAT, the in-house administrative database in the Danish Medicines Agency; Finland (FI): in-house register for marketing authorisations, Fimea; Norway (NO): Athene, in-house database at the Norwegian Medicines Agency, version 2019.09.1.; and Sweden (SE): VARA, available at the Swedish eHealth Agency.

Table 1 The source data for this study, from the Annex of the 10-year report to the EC (EMA/35987/2016), listing new authorised medicines (Annex' chapter 1)[4]

Annex table number*	Tables in the Annex of EMA'S 10-year report	Number of medicinal products listed
1	New medicines (CAPs, initial MAs, including a paediatric indication (product group A)†	82
3	New pharmaceutical forms (or routes of administration) of paediatric relevance (CAPs, line extensions of existing MAs) (product group B)	27
6	New pharmaceutical forms (or routes of administration) of paediatric relevance (NAPs, line extensions of existing MAs) (product group B)	16

*Annex' table 4, listing new nationally authorised medicines, was excluded since the majority were generic products and not new medicinal products. Annex' tables 2 and 5 (new paediatric indications, variations of already authorised products) were not analysed since our focus was on availability of new products.
†Annex' table 1 excludes medicines that are not subjected to the obligations of the Paediatric Regulation (eg, generics, hybrid medicines, biosimilars, etc).
CAPs, centrally authorised products; EC, European Commission; EMA, European Medicines Agency; MA, marketing authorisation; NAPs, nationally authorised products .

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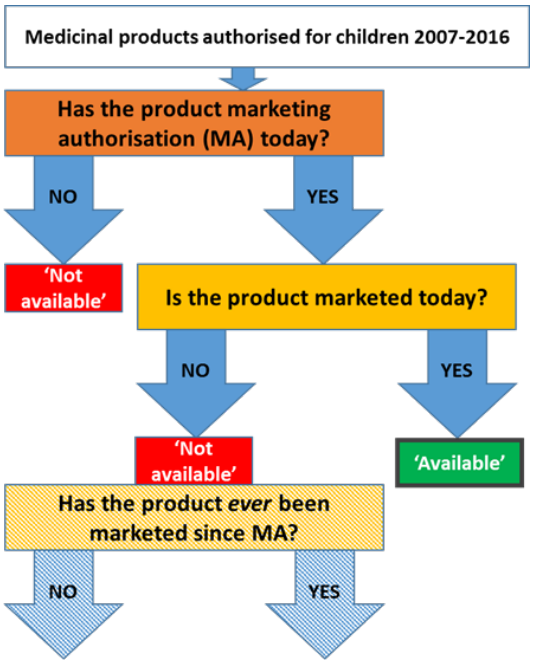

Figure 1 Flow chart illustrating how marketing status was assessed for the individual products. MA, marketing authorisation.

Marketing status was assessed separately for each country. Each medicinal product listed in the Annex tables was classified by the following two criteria: (1) having a valid MA or not, and (2) being marketed or not (figure 1). For the new formulations (product group B), if products were assessed as 'not marketed', the additional information regarding whether the product had ever been marketed between 2007 and 2016 was collected, where data were available. This information was accessible in three (DK, FI and NO) national databases, and not analysed for SE.

The Paediatric Regulation may require companies to develop age-appropriate formulations in addition to what is foreseen for use in adults, specified in the agreed-upon PIP. To analyse whether these obligations exerted any impact on the marketing status of new formulations, the agreed-upon PIPs were assessed regarding whether the formulation was part of the obligations in the PIP. The new formulations (product group B) with an agreed-upon PIP were identified using the information from the EMA's database.[12]

Data analysis

Results were calculated as percentages (proportions) of the new products which still had a valid MA and being marketed. Data were presented both in terms of the sums of all countries and separately for each country. Distributions between different therapeutic areas were identified according to the Anatomical Therapeutic Chemical code provided in the corresponding Summary of Product Characteristics. Descriptive tables, figures and statistics were created in MS Excel.

Several of the products in the source lists represent more than one strength or form. For new medicinal products (product group A), a separate assessment was initially performed for each strength. In the final analysis of these products, a new medicinal product was regarded as 'marketed' even if not all different strengths were placed on market. For the product group B, separate assessment was performed for each form or strength for the new formulations.

The products presented in this study by substance and pharmaceutical form because of possible variations in the product trade names between countries.

RESULTS

New centrally authorised medicinal products (product group A)

Products still having a MA and being marketed

Over 90% (76/82) of the new paediatric medicinal products authorised centrally between 2007 and 2016 still retained MA at the time of the study (Q1/2019). Out of these 76 newly authorised medicinal products, the most common group was medicines for infections and vaccines (30%) (table 2). More than one-third (27/76) of new medicinal products had several strengths initially authorised, and for nearly all of these (23/27), all strengths were marketed.

Products not marketed

A total of six medicinal products had no longer marketing authorisation in the EU at the time of the study. These products contained gadoversetamide, rilonacept, influenza vaccine (live attenuated, nasal), somatropin, lamivudine/raltegravir potassium and pancreas powder. One of these products (gadoversetamide) was withdrawn based on safety signals. The reason for the withdrawal of the other products (N=5) is not stated in the databases used.

Nearly half of the antineoplastic and immunosuppressive agents were not marketed in any of the Nordic countries. There were additional differences between the countries, regarding distribution among therapeutic areas: in FI, 4/10 of the products in the group of bile enzymes, vitamins and medicines for metabolic disease were not marketed; conversely, in the other countries, the proportion was 1/10. Similarly, as much as 5/11 of anticoagulants, coagulation factors and other haematological agents were not marketed in FI, but in other countries, the proportion was lower: 4/11 in SE and 2/11 in both NO and DK (table 2).

A total of 29 medicinal products were not marketed in at least one of the included countries (table 3). The hydroxycarbamide and cholic acid products are examples of the 13 new medicinal products that were not marketed in any of the Nordic countries.

On average, 57/76 of the newly authorised medicinal products were currently being marketed in the Nordic countries. SE had the highest proportion (79%), followed by NO (78%), DK (74%) and FI (68%) (figure 2).

New formulations (product group B)

A total of 43 products represented new formulations, of which 27 were centrally authorised, and 16 nationally authorised. Five of the nationally authorised products were excluded due to insufficient information, rendering

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Table 2 New centrally authorised medicinal products (n=76) having MA and being marketed across different therapeutic areas as defined by ATC codes and number of medicinal products in DK, FI, NO and SE

Therapeutic area (ATC codes)	Total number of new medicinal products	Number of medical products being marketed			
		DK	FI	NO	SE
Antibacterial, antimycotic, anti-HIV agents, vaccines and immunoglobulins (J01, J02, J05, J06 and J07)	23	14	17	17	18
Antineoplastic and immunosuppressive agents (L01, L03 nd L04)	11	7	6	6	7
Anticoagulants, coagulation factors and other haematological agents (B01, B02 and B06)	11	9	6	9	7
Bile enzymes, vitamins and metabolic disease (A05, A11 and A16)	10	9	6	9	9
Antiepileptics, sleeping agents and mitochondrial diseases (N03, N05 and N06)	7	7	7	7	7
Allergy, asthmatic and cystic fibrosis agents (R01, R03 and R07)	4	4	3	4	4
Antihypertensives and hyperlipidic agents (C02, C07 and C10)	3	2	3	3	3
Antipoisoning agents (V03)	2	1	1	1	1
Contraceptives (G03)	1	1	1	1	1
Duchenne muscular dystrophy (M09)	1	1	1	1	1
Growth hormone (H01)	1	1	1	1	1
Topical antibiotics (D06)	1	0	0	0	1
Antimalarial agents (P01)	1	0	0	0	0
All (ATC A-V)	**76**	**56**	**52**	**59**	**60**

ATC, Anatomical Therapeutic Chemical; DK, Denmark; FI, Finland; MA, marketing authorisation; NO, Norway; SE, Sweden.

it impossible to identify the exact product. The resulting 38 products with new formulations, represented a total of 56 different formulations, as several strengths or forms were relevant for some products. Each of these 56 formulations were assessed by marketing status.

Figure 3 indicates the marketing status in the various countries for these 56 products. In all four countries, the majority (91% to 95%) still had MA. However, the proportion of products being marketed was substantially lower, ranging from 50% to 71%. SE had the highest proportion of products marketed, and NO had the lowest. The proportion of marketed products was lowest for nationally authorised products (ranging from 38% to 62%), showing lowest proportion in Finland.

One fourth (14/56) of the different specific formulations were not marketed in any of these countries, and 29% (16/56) were marketed in all countries. Table 4 lists details of the 40 formulations that were not marketed in one or more of the countries, having antivirals as the largest group of such products. Most of the new formulations that were not marketed, seem never to have been marketed (*).

The formulations not marketed in any country were often the paediatric specific, such as the lower strength formulations (5/14), the oral liquid/powder/granules (5/14) and the chewable tablets (2/14). Conversely, approximately half of the products marketed in all countries were products for which the new formulation seemed to have replaced the old one (eg, prefilled syringe replacing vials, tablets replacing capsules and 'ready-to-use solution for injection' replacing 'powder and solvent for solution for injection').

The majority (35/56) of the reviewed new formulations represented products with agreed-upon PIPs where the specific formulation was part of the PIP obligations. Only 6 of these 35 formulations were marketed in all countries. Of the 14 formulations not marketed in any of the countries, nine were listed as specific requirements in the PIP. In contrast, the majority (10/16) of the formulations available in all countries, did not have a PIP or were not included in specific PIP formulation requirements.

DISCUSSION

Our data reveal that on average 75% of the new paediatric medicines initially authorised for children (2007–2016) were still authorised and marketed. Similarly, for the new paediatric formulations, 57% were marketed.

The reported achievements of the Paediatric Regulation[3 4] are optimistic, indicating increased number of authorised medicines for children. However, the choice to place an authorised product on the market in each country is influenced by several factors. Therefore, assessing the actual marketing status may add important piece of information regarding the medicines' availability

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Table 3 New medicinal products having marketing authorisation (n=76) but not marketed (marked as X in the columns) in DK, FI, NO and SE, by therapeutic area (based from ATC code at second level, eg, B02), year and country

			Products not marketed, marked with X			
Therapeutic area	**Year**	**Medicinal product**	**DK**	**FI**	**NO**	**SE**
Antihaemorrhagic	2012	Catridecacog		X		X
Antihaemorrhagic	2013	Human coagulation factor VIII/human von Willebrand factor	X	X	X	X
Antihaemorrhagic	2016	Eftrenonacog alfa		X		
Antihaemorrhagic	2016	Albutrepenonacog alfa		X		X
Antihaemorrhagic	2016	Human coagulation factor X	X	X	X	X
Anti-infective agent for topical use	2007	Retapamulin	X	X	X	
Antineoplastic agent	2007	Nelarabine			X	
Antineoplastic agent	2007	Hydroxycarbamide	X	X	X	X
Antineoplastic agent	2016	Asparaginase	X	X	X	X
Antipoisoning agent	2007	Hydroxocobalamin	X	X	X	X
Bile and liver diseases	2014	Cholic acid	X	X	X	X
Hypertension	2013	Bosentan	X			
Immunoglobulins	2007	Human normal immunoglobulin (IVIG)	X	X	X	
Immunosuppressants	2009	Canakinumab		X		
Immunstimulating	2013	Filgrastim	X	X	X	X
Immunstimulating	2016	Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	X	X	X	X
Malaria	2011	Dihydroartemisinin / piperaquine phosphate	X	X	X	X
Metabolic disease	2008	Sapropterin		X		
Metabolic disease	2014	Elosulfase alfa		X		
Respiratory tract disease	2012	Ivacaftor		X		
Vaccine	2007	Human papillomavirus vaccine (types 16–18)	X			X
Vaccine	2009	Pneumoccocal polysaccharide conjugate vaccine (absorbed)	X		X	
Vaccine	2012	Repandemic influenza vaccine (H5N1) (whole virion, inactivated and prepared in cell culture)	X	X	X	X
Vaccine	2013	Diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed)	X	X		
Vaccine	2013	Influenza vaccine (live attenuated, nasal)	X			
Vaccine	2013	Diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and Hib conjugate vaccine (adsorbed)	X	X	X	X
Vaccine	2016	Pandemic influenza vaccine (H5N1) (live attenuated, nasal)	X	X	X	X
Vaccine	2016	Diphtheria, tetanus, pertussis (acellular, component), hepatitis b (rDNA), poliomyelitis (inactivated) and Hib conjugate vaccine (adsorbed)	X	X	X	X
Vitamin	2009	Tocofersolan d-alpha tocopheryl polyethylene glycol succinate		X		
Number of all medicinal products not marketed			**20**	**24**	**17**	**16**

ATC, Anatomical Therapeutic Chemical; DK, Denmark; FI, Finland; NO, Norway; SE, Sweden.

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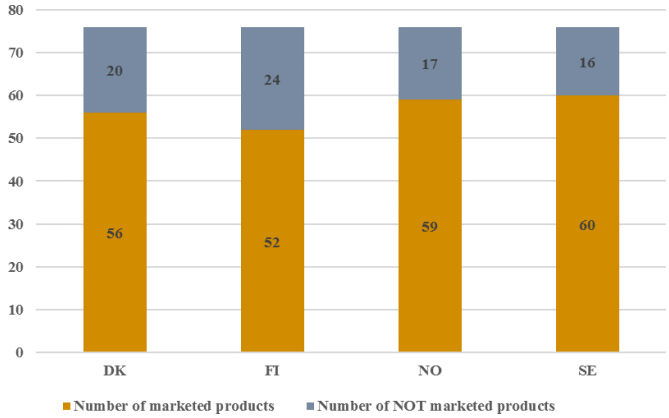

Figure 2 Number of new medicinal products marketed (or not) in DK, FI, NO and SE. DK, Denmark; FI, Finland; NO, Norway; SE, Sweden.

for children. Some papers have studied the availability of, for example, paediatric oral formulations and shown variability across Europe[13–15] but, unfortunately, none of these studies have assessed the availability related to the reported outcome of the Paediatric Regulation.

For the new medicines initially authorised for children, the divergence between countries was not profound. These new medicines were all centrally authorised, which would facilitate to market these products 'Europe-wide', targeting the largest possible population throughout Europe.

Despite child-friendly, age-appropriate formulations being especially important for the youngest age groups, for three of the four countries only roughly half of the new formulations were marketed. It is notable that the forms or strengths that were not marketed in *any* country were often the paediatric-specific ones: lower strengths, oral liquids or chewable tablets. In contrast, a significant proportion of the new forms and strengths that were marketed in *all* countries did not seem to fulfil a specific paediatric need but rather appeared to optimise the entire product line, often replacing old formulations.

The reasons why products were placed on or not placed, or taken off the markets, were not assessed in this study. Intuitively, the limited size of the population could anticipate sparse return on investments, targeting only a fraction of the patients. Regulatory obligations, like nation-specific packages, in addition to the national pricing and reimbursement systems may have strong effect on the strategic marketing decisions. Furthermore, prescribing habits may play a role, particularly, if the established practice of off-label use has been accepted for decades. Finally, there might be some dissimilarities in the unmet therapeutic needs between the countries (eg, antivirals not marketed due to the smaller number of children affected).

The Paediatric Regulation requirements to develop a paediatric specific formulations, as agreed in the PIP, are no indicator of whether the formulation will be marketed. Only 17% of the new formulations agreed on PIP, were marketed in all four countries, and almost 2/3 of the formulations that were not marketed in any country were specifically requested in the PIPs. Importantly, the reward granted through the regulation does not oblige the company to place a product on the market in all countries, but only to have MA in all member states. Marketing is, therefore, not specifically motivated, and any potential reward (ie, prolonged protection) is granted nationally for the full product line regardless of whether all paediatric-specific formulations are marketed in that country.

Our data indicates that most products that were not currently marketed had *never* been marketed, suggesting that the decision to entering a country-specific market is made up front. Thus, factors like actual low sale, patent

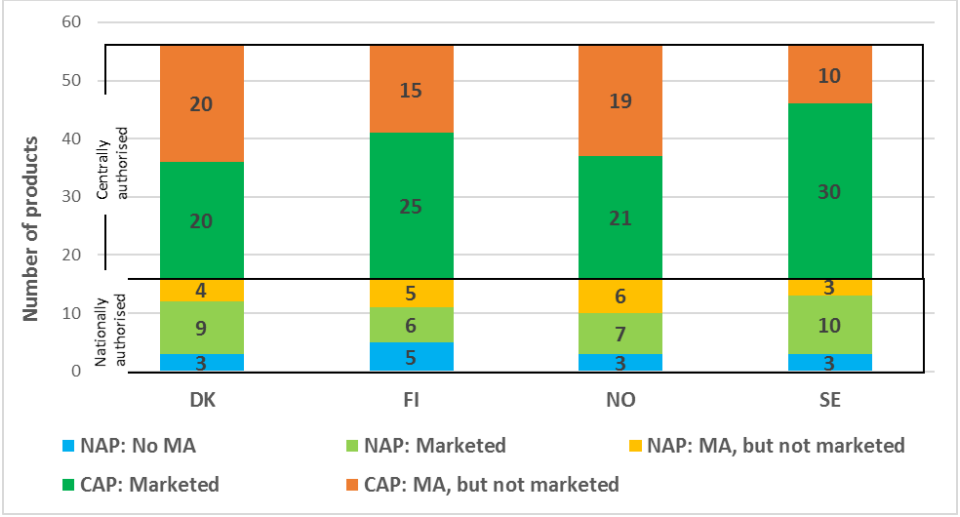

Figure 3 Marketing status for new formulations of medicinal products (whether the product still had MA and was still marketed) per country (DK, FI, NO and SE). CAP, centrally authorised product; DK, Denmark; FI, Finland; MA, marketing authorisation; NAP, nationally authorised product; NO, Norway; SE, Sweden.

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Table 4 New pharmaceutical forms and strengths not marketed in DK, FI, NO and SE by year of MA, therapeutic area and country

Therapeutic area	Year	Medicinal product	Formulation	Product not marketed, marked with X (never been marketed since MA*; DK, FI, NO—No data available for SE)			
				DK	FI	NO	SE
Agents acting on the renin–angiotensin system	2009	Losartan	Powder for oral suspension	X	X		X
Analgesic drugs	2011	Rizatriptan	Melt tablet/ oral lyophilisate 5 mg		X*	X*	
Antihaemorrhagic drugs	2007	Nonacog alfa	Powder and solvent for solution for injection, 250 IU	X*	X*	X*	
Antihaemorrhagic drugs	2016	Eltrombopag/olamine	Tablet 12.5 mg	X*	X*	X*	X
Antihaemorrhagic drugs	2016	Eltrombopagolamine	Powder for oral suspension formulation 25 mg	X*	X*	X*	X
Antihistamins (systemic)	2007	Desloratadine	Orodispersible tablets, 2,5 mg	X*			
Antihistamins (systemic)	2007	Desloratadine	Orodispersible tablets, 5 mg	X*		X*	
Antihistamins (systemic)	2012	Rupatadine	Oral solution	X	X		X
Anti-inflammatory and antirheumatic drugs	2011	Ibuprofen	Oral suspension	X	X*	X	
Antineoplastic drugs	2009	Temozolomide	Powder for solution for infusion	X*			
Antipoisoning agent	2007	Deferiprone	Oral solution 100 mg/mL.	X			
Antiviral drugs	2015	Ritonavir	Oral powder	X*	X*	X*	
Antiviral drugs	2016	Atazanavir/sulfate	Oral powder 50 mg	X*	X	X*	X
Antiviral drugs	2009	Tipranavir	Oral solution	X*	X*	X*	X
Antiviral drugs	2012	Darunavir	Oral suspension 100 mg/mL			X*	
Antiviral drugs	2012	Tenofovir disoproxil as fumarate	150 mg film-coated tablet (123 mg tenofovir disoproxil)			X*	
Antiviral drugs	2012	Tenofovir disoproxil as fumarate	200 mg film-coated tablet (163 mg tenofovir disoproxil)			X*	
Antiviral drugs	2012	Tenofovir disoproxil as fumarate	250 mg film-coated tablet (204 mg Tenofovir disoproxil)			X*	
Antiviral drugs	2012	Tenofovir disoproxil as fumarate	Granules 40 mg/g (33 mg/g tenofovir disoproxil)			X*	
Antiviral drugs	2011	Nevirapine	50 mg prolonged-release tablet	X*	X*	X*	X
Antiviral drugs	2011	Nevirapine	100 mg prolonged-release tablet	X*	X*	X*	X
Antiviral drugs	2013	Etravirine	Tablet 25 mg strength	X*	X*	X*	X
Antiviral drugs	2011	Oseltamivir	Powder for oral suspension 6 mg/mL	X*		X*	
Antiviral drugs	2013	Raltegravir	Chewable tablets 100 mg	X*			
Antiviral drugs	2013	Raltegravir	Chewable tablets 25 mg	X*			

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Table 4 Continued

Therapeutic area	Year	Medicinal product	Formulation	Product not marketed, marked with X (never been marketed since MA*; DK, FI, NO—No data available for SE)			
				DK	FI	NO	SE
Antiviral drugs	2014	Raltegravir	Granules for oral suspension	X*	X*	X*	X
Drugs for obstructive airway diseases	2009	Montelukast	Granules			X	
Drugs used in diabetes	2010	Insulin glulisine	Intravenous use	X*			
Drugs used in diabetes	2009	Metformin HCl	Powder for oral solution in sachets	X*	X*	X*	X
Immunostimulants drugs	2013	Peginterferon alfa-2a	Prefilled syringe 90 µg	X*	X*	X*	X
Immunosuppressant drugs	2011	Mycophenolate mofetil	Hard capsules 250 mg	X*	X*	X*	X
Lipid modifying agents	2010	Atorvastatin	Chewable tablets 5 mg	X*	X*	X*	X
Lipid modifying agents	2010	Atorvastatin	Chewable tablets 40 mg	X*	X*	X*	X
Lipid modifying agents	2010	Atorvastatin	Chewable tablets 10 mg			X*	
Lipid modifying agents	2010	Atorvastatin	Chewable tablets 20 mg		X*	X*	
Other respiratory products	2015	Ivacaftor	Granules 50 mg		X*		
Other respiratory products	2015	Ivacaftor	Granules 75 mg		X*		
Psychoanaleptics	2014	Atomoxetine	Oral solution		X*		
Vaccines	2008	Rotavirus vaccine, live	Oral suspension/liquid		X*		
Vaccines	2011	DTP/Hib/Polio vaccine	Prefilled syringe	X*	X*	X	X
Number of new forms and strengths not marketed				**27**	**25**	**28**	**16**

DK, Denmark; FI, Finland; NO, Norway; SE, Sweden.

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expiration or introduction of generics seem of limited relevance.

Strengths and limitations

In this study, a product being 'marketed' is interpreted as a surrogate measure for the product's availability after it has been placed on the market, because it does not guarantee the access to patients. Medicines can be available for the patients even if a product is not marketed (eg, through special licensing or compassionate use programmes), and despite a product is marketed, it may not be available for patients (eg, reimbursement rules, medicine shortages or physicians not prescribing the product).

There are several extremely relevant factors having direct impact on the companies' market strategies and for the decisions to placing products on markets, such as the targeted market size or country specific expenditure, pricing and reimbursement practices. If thoroughly investigated, this type of additional data would give more detailed rationale and increase understanding for the current situation. However, studying these aspects would need the involvement of other scientific disciplines and other regulatory authorities.

This study did not assess the clinical consequences of the marketing status of each product and whether these products specifically fulfil a certain paediatric unmet need or not. For some products, alternatives might have been available, for others not. It is assumed that at least for products with a PIP obligation, such a need has been identified.

Some limitations were identified for the source data, as the nationally authorised products were reported on voluntary basis by National Competent Authorities and thus may not be complete. Additionally, for the nationally authorised products, generics seem to have been reported extensively, which was the reason why the Annex' table 4 was excluded. Nevertheless, the listed products are expected to represent most of the relevant ones authorised.

Placing a product on the market and having it marketed increases the potential availability, ensures access to national product information, provides proper follow-up by companies and authorities, and frequently affects the price regulation and therefore serves as important indicator of the accessibility. This study provides a snapshot of the 'real-world' situation at a specific time point and will not fully reflect all the dynamic factors and processes related to marketing status.

While acknowledging that several factors ultimately impact patient 'real-life' access to medicines, we consider having a product marketed as one particularly important indicator of the medicine availability.

These results may not be typical for all European countries since it represents a group of relatively small countries and, as such, a market with limited financial interest. Therefore, similar data from other countries would be needed to create a better picture of the overall situation.

In conclusion, the reported success of the Paediatric Regulation in terms of new authorised products, is only partially valid. To make more sustainable future changes to the current situation, the ongoing EC pharma strategy, including the evaluation of Paediatric Regulation,[16] should consider more carefully to understand reasons and cure the existing hindering factors. Elements like targeted rewards, adapted legal requirements, an alternative pricing system and decreasing off-label use should all be discussed. Truly, the access to medicines for children is in practice still limited.

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Patient consent for publication Not required.

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