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Report on the survey of all paediatric uses of medicinal products in Europe

Established according to article 42-43 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for Paediatric use

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1. Introduction

Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use (hereafter referred as the "Paediatric Regulation") aims to facilitate the development and accessibility of medicinal products for the paediatric population and to ensure that medicinal products used to treat children are subject to high quality research and are appropriately authorised for use in the paediatric population.

One of the legal requirements of the Paediatric Regulation is the collection of available data on all existing uses of medicinal products in the paediatric population. In accordance with art. 42 of the Regulation, the PDCO provided on 26 October 2007 a guideline on the content and format of the data which had to be collected by the 27 EU Member States[1]. The 3 EEA states which are not EU Member States(Iceland, Norway and Liechtenstein) were also invited to provide data.

The guideline emphasized the need to collect data on all existing uses of medicinal products in the paediatric population (use of authorised medicinal products within the terms of the marketing authorisation, use of authorised medicinal products outside the terms of the marketing authorisation and of the summary of the product characteristics-so-called *off-label use*- and use of unauthorised medicinal products) for the purpose of establishing the unmet needs at the EU level. It was mentioned that the off-label use and the unauthorised use of medicinal products was of paramount interest for identifying the paediatric needs. For communicating the data to the European Medicines Agency, a structured electronic format with a single table should have been used.

The expectations of the survey were to provide general statistics on the frequency and extent of use, taking into account public health priorities. At the same time, knowing that Member States might have different sources of information and tools to collect information, it was expected that the supplied data would have some degree of heterogeneity as well as a different level of detail and completeness.

1 http://www.ema.europa.eu/pdfs/human/paediatrics/5756962007en.pdf

2. Methodology

2.1. Description of data by country

2.1.1. Austria

The submitted data were collected during a two year period (2005-2006) from the following sources: social security-, hospital pharmacy-, over-the-counter panel- and pharmacovigilance databases of the Austrian Agency for Health and Food Safety (AGES). The data coverage included all medicinal products prescribed in outpatients and reimbursed by the state health insurance (with exception of medicines with a sales price lower than the minimum deductible threshold). Reports of medicinal products approved for dispensing in individual cases, some Austrian hospital prescriptions (inpatients) and pharmacovigilance data based on individual safety case reports were also included. Off-label status of the prescriptions - related information was provided (where available). No structured information was available regarding the corresponding disease, route of administration, dosing, treatment duration and authorised indication. Information on the pharmaceutical form was available for most products.

The extent of use was quantified by the number of packages used (for the inpatient data) and the number of paediatric patients treated for each INN (for the outpatient data).

2.1.2. Belgium

Belgian data were collected from a single paediatric hospital (inpatients); outpatient data were not reported. The timeframe for the data acquisition was not mentioned. Information regarding the treated medical condition and to the unauthorised and off-label use of the medicinal products was provided in most cases.

There was no quantitative measurement of the extent of use of medicines in the paediatric population.

Therefore a surrogate of the extent of use was analysed, namely the frequency of appearance of the medicinal products belonging to various ATC classes in the submitted database.

2.1.3. Bulgaria

Submitted information was scarce and heterogeneous. Data were collected from two paediatric hospitals from the Bulgarian capital during different periods of time (ranging from 3 months to 12 months). Off-label use information only was reported.

No estimation of the extent of use was provided.

2.1.4. Cyprus

Collected data originate from two sources: the Cypriot Paediatric Association (private hospital data) and the paediatric database of the biggest hospital in Cyprus (treating over half of all paediatric inpatients in the country). Overall information was scarce. The period of time for the data collection was not mentioned. Data regarding the off-label and unauthorised use were provided.

An attempt to quantify the extent of the paediatric use was made by providing the number of patients treated with a defined dose over a defined period of time.

2.1.5. Denmark

The Danish dataset referred to the primary health care sector and included information on medicinal products sold to outpatients, dispensed by doctors in private practices and constituting medicine stocks at various Danish medical institutions. Inpatients data were drawn up based on reports from hospital pharmacies and from the Danish State Serum Institute. Age-related information was provided; of note, the reported age groups were not those recommended by the ICH E11 guideline. Information on the compassionate use of medicines in inpatients was provided in an additional dataset, where ICH E11 - compliant age group information was also included.

Extent of use was measured by cost data (turnover based on current medicine prices) in the primary health and in the hospital sectors; quantities were expressed in DDD (defined daily doses).

2.1.6. Estonia

The Estonian data were collected via a cross-sectional drug utilisation study based on a national prescription database. All dispensed prescriptions to paediatric subjects during 2007 were analysed. The summaries of product characteristics of the medicinal products were reviewed to extract the paediatric information. The submitted data focus on the off-label use of medicines.

2.1.7. Finland

The Finnish data were collected from a university hospital pharmacy database for a two-year period (2006-2007) and from the Finnish Social Insurance Institute database, queried over a one-year period (2007). Submitted pharmacovigilance data were limited and were obtained from the adverse events registry of the Finnish National Agency for Medicines. Data referring to blood products, haemostatic glues, sponges containing medicinal products, products for nutrition and fluid balance, products intended for dialysis and contrast media were not collected. The off-label status of the medicinal product was mostly available. ATC codes (not required by the guideline) were provided. It was not possible to analyse age-related data because of the significant overlapping of the reported paediatric age groups. Furthermore, extensive text processing was needed before the data analysis.

There was no quantitative estimation of the extent of use.

2.1.8. France

Information on the different types of uses of medicinal products in children was provided: unauthorised use in children, corresponding to a national compassionate use (called "temporary authorised use" in France) and off-label use. The latter was divided in use of extemporaneous preparations, and off-label use in inpatients. Information on the authorised use in outpatients was also provided. Data were collected from the National Health Products Agency (database for compassionate use, database for extemporaneous preparations), from one public paediatric hospital database and from a private international database on outpatient dispensing (the IMS Health database). The data coverage varied from 6 month to 5 years, depending on the database.

A quantitative measurement of the extent of use was provided for in-hospital use, for which the daily number of prescriptions was reported.

2.1.9. Hungary

Submitted data were collected from the National Institute of Pharmacy and from the National Health Insurance Fund (the latter dataset contained outpatient data). Two additional lists set up by the

Hungarian College of Paediatrics containing the list of medicinal products used off-label and the paediatric use in haematology were also provided. The data covered a period of two years. ATC-related data was provided (not requested by the guideline), while age-related data was provided for one data subset only.

The quantitative measurement of the extent of use was cost data (number of sold units, retail price per unit, covered period of time).

2.1.10. Iceland

Data were collected from the Icelandic National Database on Drugs Prescribed and Dispensed for Children (data coverage: 6 months). Age- and ATC-related information was provided. Information regarding the regulatory status of medicinal products (unauthorised/off-label) and regarding the condition requiring treatment was not provided.

The quantitative measure of the extent of use was the defined daily doses (DDD's) for each ATC code.

2.1.11. Republic of Ireland

Irish data were obtained from a survey of unauthorised and off-label use of medicinal products in the paediatric population. Medicinal products used unauthorised or off-label in children were identified by collecting data from hospital and non-hospital based paediatricians countrywide and by visiting paediatric hospital pharmacies. Age-related information was provided.

No measurement of the extent of use data was provided.

2.1.12. Lithuania

Data were collected from the database of one university hospital pharmacy. Age- and condition-related information was provided. No difference between authorised and unauthorised or off-label use was made (both types of use reported together).

There was no quantitative estimation on the extent of use available.

2.1.13. Latvia

Data were collected from the pharmacy databases of two paediatric hospitals. Both authorised and off-label use of medicines was reported. Trade names of the medicinal products and corresponding ATC-related information was provided.

No quantitative estimation on the extent of use was provided.

2.1.14. Malta

Information on medicines used in the paediatric population was provided by using the existing data from the government hospitals pharmacy list. Indications and dosage recommendations were made according to the British National Formulary for Children, which is widely used as a reference source by the Maltese healthcare professionals.

2.1.15. The Netherlands

Data were collected by conducting a survey covering most existing pharmacies in the Netherlands over a 2-year period. Age- and ATC-related information was provided. A report on the off-label use of medicines in The Netherlands, created in 2007 after analysing a survey carried out among general

practitioners and health care specialists and a study of existing professional guidelines for physicians was additionally submitted. The report is a mix of paediatric and adult data and was submitted in its original Dutch version. It is not reflected in the present analysis.

The survey data contain the number of prescriptions per ATC as a quantitative measure of the extent of use.

2.1.16. Norway

The Norwegian dataset was collected from two sources: the national prescription registry (outpatient data) and the hospital pharmacies sales registry to all Norwegian neonatology and paediatric units (inpatient data). The data coverage period was one year. Data collected from the prescription registry contained age-, and regulatory status (off-label/unauthorised) related information. Age-related data collected from the hospital sales registry did not allow for grouping information. Information on indication, dosage regimen and route of administration was not available.

Extent of use was reported as DDD (if available) and as number of units per product (tablets, ampoules etc. - for those medicines without defined DDD).

2.1.17. Portugal

Submitted data were collected from a survey involving 22 hospitals and refer to inpatients only. Off-label status related information was available in 33% of the cases. Age-related data could not be processed due to extreme heterogeneity. Extensive processing of submitted dataset before analysis was necessary.

There was no estimation of the extent of use of the medicinal products available.

2.1.18. Romania

Data were collected from several hospital databases countrywide (inpatients). Age-related information was not constantly reported. Data coverage period was not mentioned. Off-label status was provided.

No direct quantitative estimation of the extent of use data was provided, but it was possible to estimate the extent of use based on the submitted data.

2.1.19. Slovenia

Data were collected by conducting a one-day-survey on the use of the medicinal products in the paediatric population, both in hospital and in the ambulatory settings. Age-, condition- and dose-related information, as well as data related to the regulatory status of the medicine (unauthorised/off-label) were provided.

There was no quantitative estimation of the extent of use in the paediatric population.

2.1.20. Sweden

Different datasets were submitted for the over-the-counter use of medicines, for the prescriptions dispensed in outpatients (with a special reference to the off-label use) and for the paediatric medicines use at Swedish hospitals.

a) OTC medicines use estimation relied on three different sources over a 2-year period: the Swedish Pharmacies Database and two questionnaires addressing two paediatric subpopulations. The extent of use was approximated from the total number of packages sold

by Swedish pharmacies. The first questionnaire aimed to measure the use of OTC medicines in Stockholm; the target population was a cohort of 4089 children born 1994 – 1996, which were included in the study as neonates and were followed prospectively. The second questionnaire documented the use of medicines (including OTC) prior to presentation to an Emergency Department (ED).

The quantitative measurement of the extent of use was the number of packages sold to children (of note, this number was estimated via a conversion factor)

b) Off-label use data in paediatric outpatients were collected by conducting a countrywide cross-sectional study over a one-year period. The Swedish Prescribed Drug Register (SPDR) provided information with regard to the identification of the medicinal product, the date of birth of the patient and the sold quantities for each medicinal product. Information about the treated conditions (diseases) was not submitted. Submitted data were restricted to medicines dispensed more than 100 times during the study year.

c) The extent of use of the medicinal products in the paediatric inpatients care was estimated by conducting a national cross-sectional point prevalence study. More than 40 hospital departments participated and the dataset referred to more than 70% of all hospitalized children in Sweden. Data collection was performed via prescription form. This requested demographic information as well as information on the medicinal products: indication, strength, dosage, form and route of administration. All medicinal products were classified according to their regulatory status into authorised, off-label or unauthorised.

Patients were divided into four groups: neonates (from birth to less than one month), infants (from month to less than one year), children (from one year to less than 12 years) and adolescents (from 12 years to less than 18 years).

2.1.21. United Kingdom

The United Kingdom provided data on the use of medicines in the paediatric population by using a reference source, the British National Formulary for Children (BNFC). The BNFC is established by the Paediatric Formulary Committee. Expert clinical advisers are used "to advise on the use of unlicensed medicines or of licensed medicines for unlicensed uses ('off-label' use)"[2].

There was therefore no estimation of the existing use (both authorised and unauthorised/off-label) of paediatric medicines in the UK.

2.1.22. Countries not submitting data

Table 1 lists the EEA countries which did not submit the requested data. Of note, almost 50% of the European paediatric population was not covered by the centralised data. This is partly explained by the fact that some countries with a large population did not submit data to the EMA.

[2] From http://bnfc.org/bnfc/bnfc/2009/202098.htm, accessed on 5 March 2010.

2.2. Overall data extent and quality

Overall, data was submitted by 22 (20 EU and 2 non EU) out of the 30 countries invited to participate. Table 1 is an overview of the compatibility of the submitted data with the Paediatric Committee recommendations.

Table 1. Compatibility of data submitted by the EEA Member States with EMA PDCO guidelines recommendations

Compatible with guideline requirements	EU Member State[3]	% Member State from EEA Population[4]
Did not submit any data	DE	16.54
	IT	11.48
	ES	9.08
	PL	7.64
	CZ	2.06
	SK	1.08
	LU	0.10
	LI	0.01
Subtotal		**47.99**
Data submitted but not compatible with PDCO guideline	UK	12.11
	NL	3.29
	EL	2.24
	SE	1.84
	BG	1.52
	LT	0.68
	LV	0.46
	MT	0.08
	IS	0.06
Subtotal		**22.29**
Data submitted and compatible with PDCO guideline	FR	12.77
	RO	4.31
	BE	2.14
	PT	2.08

[3] From http://publications.europa.eu/code/pdf/370000en.htm
[4] Population data from http://europa.eu/abc/european_countries/index_en.htm

	HU	2.02
	AT	1.66
	DK	1.08
	FI	1.06
	NO	0.94
	IE	0.80
	SI	0.40
	EE	0.28
	CY	0.16
Subtotal		**29.72**
Total		**100**

Submitted datasets were heterogeneous and did not include information about the data representativeness for each country's paediatric population (with some datasets obviously being not representative). Partial translation into English was necessary for about 25% of the submitted data. Many datasets did not include a quantitative measurement of the extent of use of the medicinal products. Sources for submitted data were always mentioned, with more than one source (hospital pharmacy, social security data, compassionate use, other sources) having been used for the majority of the datasets.

3. Data analysis

3.1. Data analysis by country

3.1.1. Austria

3.1.1.1. Unauthorised medicinal products used in children

The dataset regarding the use of unauthorised products was analysed by the following criteria: product name, age group (ICH classification), ATC codes (where available).

3.1.1.1.1. Name of unauthorised medicinal product

The most frequent medicinal products used unauthorised were diclofenac, followed by ACE inhibitors (ramipril) and antidepressants (citalopram and fluoxetine). Statins (simvastatin) were also frequently used unauthorised.

3.1.1.1.2. Use of unauthorised medicinal products in relation to age

The age groups distribution among children having received unauthorised medication was: newborn-11%, infants and toddlers-25%, children under the age of 12 years-32% and children older than 12 years and adolescents -32%.

The identified unauthorised medicinal products were grouped based on the first letter of the ATC codes; categories with a percentage of off-label use >5% were broken down into medicinal product therapeutic areas to give a further indication on the unmet therapeutic needs for the paediatric population.

3.1.1.1.2.1. Cardiovascular medicinal products used unauthorised (age)

This was the largest group of products used unauthorised. The most frequent used medicinal products were those acting on the renin-angiotensin system (28,8%), followed by beta-blockers(12,3%). The most frequently used individual products were ramipril, lisinopril and isosorbid mononitrate.

3.1.1.1.2.2. Nervous system medicinal products used unauthorised (age)

The second largest group of products used unauthorised in children was the group of the nervous system treating medicines. Psychoanaleptics (33,6%), analgesics (31,9%), psycholeptics (14,1%) and anti-epileptics(10%) were most frequently used (individual medicinal products: citalopram, tramadol and fluoxetine).

3.1.1.1.2.3. Alimentary and metabolism medicinal products used unauthorised (age)

The proton pump inhibitors together with the H_2-receptor antagonists (29,1%) and the vitamins (26,7%) were the groups of medicinal products most frequently used unauthorised. Tocoferol and esomeprazole were the most used individual medicinal products.

3.1.1.1.2.4. Systemic antiinfectives used unauthorised (age)

Antibacterials for systemic use (72,8%), immune sera and immunoglobulins(15,3%) were frequently used unauthorised, with vancomycin and the human immunoglobulins for intravascular administration as the most frequently used individual products.

3.1.1.1.2.5. Blood and blood-forming medicinal products used unauthorised (age)

Blood and blood-forming medicinal products used unauthorised were represented by antithrombotic agents (50,5%) and blood substitutes and perfusion solutions(37,1%). Iloprost and enoxaparin were the most used individual products.

3.1.1.1.2.6. Dermatological medicinal products used unauthorised (age)

Antifungals for dermatological use (19,7%), corticosteroid dermatological preparations (14,8%), anti-acne preparations (14,5%), antiseptic and disinfectants(12,6%) and antibiotics and chemotherapeutics for dermatological use (10,4%) were most commonly used. Isotretinoin, terbinafine and povidone-iodine were the first three individual products most used unauthorised from this therapeutic class.

3.1.1.1.2.7. Respiratory system medicinal products used unauthorised (age)

Medicines for obstructive respiratory diseases (31,5%) were the more frequent subclass used, followed by cough and cold preparations (30,1%), antihistamines for systemic use (22%) and nasal preparations (10,4%). Acetylcysteine, salbutamol and cetirizine were the most frequently individual products used unauthorised.

3.1.1.2. Authorised medicinal products used in children

The dataset regarding the use of authorised products was analysed by the following criteria: product name, age group (ICH classification), ATC codes where available, patient setting (inpatients, outpatients).

3.1.1.2.1. Name of authorised medicinal product

The medicinal products used most frequent within the terms of the marketing authorisation in children were antibiotics (amoxicilline plus beta-lactamase inhibitors, clarithromycin, penicillin), multivitamins and beta-mimetics (salbutamol).

3.1.1.2.2. Use of authorised medicinal products in relation to patient setting and age

3.1.1.2.2.1. Use of authorised medicinal products in inpatient newborns (from birth to less than 28 years of age)

The medicinal products used most frequent within the terms of the marketing authorisation in inpatient term newborns were antibiotics (ampicillin and cefuroxime), phytomenadione and electrolytic solutions. For outpatient term newborns, the medicinal products with authorised use were antifungals (nystatin), antibiotics for topical use and other dermatological products for topical use.

3.1.1.2.2.2. Use of authorised medicinal products in inpatient infants and toddlers (from 28 days to less than 2 years of age)

The medicinal products used most frequent within the terms of the marketing authorisation in inpatient infants and toddlers were human immunoglobulins for intravascular administration, solutions containing lactic acid producing organisms and oral rehydration salt formulations. For outpatient infants and toddlers, antibiotics (amoxicillin plus beta-lactamase inhibitors, penicillins, clarithromycin), and antiasthmatics (montelukast, salbutamol) were used most frequent.

3.1.1.2.2.3. Use of authorised medicinal products in inpatient children (from 2 years to less than 12 years of age)

The medicinal products used most frequent within the terms of the marketing authorisation in inpatient children aged from 2 to less than 12 years were non-steroidal anti-inflammatory medicines (naproxen), beta-mimetics (salmeterol and other beta-agonists) and combinations containing sodium fluoride. Of note, the submitted dataset mainly referred to outpatients for this age group.

3.1.1.2.2.4. Use of authorised medicinal products in inpatient adolescents (from 12 years to less than 18 years of age)

The medicinal products used most frequent within the terms of the marketing authorisation in inpatient adolescents were dexpanthenol, fluoxetine and diazepam. For outpatient adolescents, antibiotics (amoxicillin plus beta-lactamase inhibitors and clarithromycin), isotretinoin and minocycline were used most frequent.

3.1.2. Belgium

3.1.2.1. Use of unauthorised medicinal products

Our analysis used the following criteria: name of the unauthorised medicine used and the pharmaceutical form of the medicinal product. Provided information refers to inpatients only.

3.1.2.1.1. Name of unauthorised medicine used

92% of the reported use of unauthorised medicinal products was noted in preterm newborns, which represented 68% of the inpatients in the submitted dataset. The most frequent mentioned medicinal products were multivitamins as solution for oral use (16%), followed by sodium ferrum gluconate complex in the same pharmaceutical form (10%) and folic acid as soft capsules (9%).

3.1.2.1.2. Pharmaceutical forms of medicinal products used unauthorised

The most frequent mentioned pharmaceutical forms used unauthorised were the solutions for injection (23,6%), followed by powders for solution for injection (11,6%), oral drops (11%) and by soft capsules (9%).

3.1.2.2. Use of off-label medicinal products

46% of the medicinal products used in the hospital pharmacies were reported as off-label. The medicines identified as used off-label were grouped according to the ATC codes. Categories with a percentage of off-label use >5% were broken down into medicinal product therapeutic areas to give a further indication on the unmet therapeutic needs for the paediatric population.

3.1.2.2.1. Alimentary and metabolism medicinal products used off-label

This was the largest ATC class used off-label (53% of the total). Plain multivitamins (16%), vitamin D and analogues (12,3%) and H2-receptor antagonists (6,2%) were most frequent mentioned off-label.

3.1.2.2.2. Blood and blood-forming medicinal products used off-label

This ATC class accounted for 20,3% of the off-label use, with oral iron supplements (9,9%), folic acid preparations (9,3%) and electrolyte solutions(1,2%) being the most mentioned substances.

3.1.2.2.3. Nervous system medicinal products used off-label

This ATC class had the third highest incidence of off-label use (approx. 10%). Antipyretic anilides (31%) and general anaesthetics (25%) were mentioned most frequent.

3.1.3. Bulgaria

A list of 25 off-label products was submitted to the EMA. The most frequent mentioned substances on this list were antihypertensives (20%), followed by hydrocortisone and diuretics (both 8%). No further analysis was possible, because of the data paucity.

3.1.4. Cyprus

Antimicrobials for intravenous use (macrolides and betalactamines plus betalactamase inhibitors) were the most common mentioned medicinal products used off-label, followed by mefenamic acid, sildenafil (for persistent pulmonary artery hypertension) and paracetamol. Injections and oral solutions were the most frequent pharmaceutical forms used off-label. Age related analysis of the off-label use was not possible.

3.1.5. Denmark

3.1.5.1. Authorised use of medicinal products

The analysis of the dataset was performed according to the following criteria: ATC class (detailed breakdown, down to level 5), age groups for the prescriptions. The following 4 paediatric age groups were predefined in the submitted dataset: from birth to less than 5 years of age, from 5 years to less than 10 years, from 10 years to less than 15 years and from 15 years to less than 18 years of age.

The most frequent used products were the anti-infectives for systemic use, followed by the products for the treatment of the sensory organs, dermatological medicinal products, respiratory system products and genitourinary system products (including sex hormones).

3.1.5.1.1. Authorised use of medicinal products in relation to age

3.1.5.1.1.1. Age group from birth to less than 5 years

The most frequent mentioned medicines used in this age group were the anti-infectives for systemic use (amoxicillin, phenoxymethylpenicillin), the respiratory medicines (salbutamol and budesonide) and the dermatological medicinal products (hydrocortisone and combinations).

3.1.5.1.1.2. Age group from 5 years to less than 10 years

The anti-infectives for systemic use (amoxicillin, phenoxymethylpenicillin) were the most mentioned medicinal products used in this age group, followed by the dermatological medicinal products (fusidic acid and hydrocortisone butyrate), the anti-infectives for topical use (fusidic acid and chloramphenicol for ophthalmic use) and the medicinal products for the treatment of the obstructive respiratory diseases (budesonide and terbutaline).

3.1.5.1.1.3. Age group from 10 years to less than 15 years

The same anti-infectives for systemic use (phenoxymethylpenicillin, dicloxacillin and amoxicillin), dermatological medicinal products (hydrocortisone butyrate and fusidic acid), respiratory system

(terbutaline and cetirizine) and ophtalmological medicinal products (chloramphenicol and levocabastine) were the most frequent mentioned medicinal products used in this age group.

3.1.5.1.1.4. Age group from 15 years to less than 18 years

The anti-infectives for systemic use (penicillin and azithromycin), the oral contraceptives (gestodene and estrogen, desorgestrel and estrogen, drospirenone and estrogen), the dermatological products (hydrocortisone butyrate and fusidic acid) and the medicinal products for the treatment of the diseases of the respiratory system (terbutaline and cetirizine) were the most frequent mentioned medicines used in this age group.

3.1.5.2. Compassionate use of medicinal products in inpatients

The most frequent medicinal products administered for compassionate use were those targeting the alimentary tract (25% of all reported use), followed by the anti-infectives for systemic use (14%) and by the medicinal products targeting the nervous system (9%). Macrogol (in combinations) was the most prescribed medicinal product, followed by benzylpenicillin and oxybutinin. The compassionate use of medicines was higher for obstipation, convulsions and infections. The highest number of prescriptions was observed in the age group from 2 years to less than 12 years of age.

3.1.6. Estonia

A total of 467.334 prescriptions dispensed to 151.476 paediatric subjects were identified within the background population of 277.265 (crude 1-year prevalence 54.6%). The prescription rate was 1700/1000 children. A total of 851 products with 309 unique active substances or combinations were prescribed.

3.1.6.1. Off-label medicinal products

31% of the prescriptions were for an off-label use; 29% of those did not have any paediatric information in the summary of the product characteristics (SmPC). 227 prescriptions (0.05%) referred to six products that had no marketing authorization in Estonia.

The percentage of off-label prescriptions due to the lack of data in SPCs was highest in the genitourinary drugs group (97%), followed by dermatological (74%) and cardiovascular drugs (61%). The proportion of off-label prescriptions due to the contraindication was highest amongst the musculo-skeletal (69%) and nervous system (16%) drugs.

Compared with topical drugs a markedly larger proportion of systemic agents (more than 60% in all age categories and over 90% of prescriptions for children from 2 to under 6 years of age) were labelled for children. The proportion of off-label topical drugs was highest for children below 2 years of age and for adolescents.

The most commonly prescribed off-label products came from the frequently prescribed ATC groups and are presented in the following table:

Drug prescription rate (per 1000 children) in different age categories

	0-1.99 years (n=29805)			2-5.99 years (n=53105)			6-11.99 years (n=74044)			12-18.99 years (n=120311)			
	Labelled	Off-label		Labelled	Off-label		Labelled	Off-label		Labelled	Off-label		
		No data	CRI*		No data	CRI*		No data	CRI*		No data	CRI*	Total No of prescriptions
Alimentary	3	20	2	5	14	2	11	18	0.5	35	22	4	11360
Blood	140	0.8	0	16	0.6	0	0.2	0.5	0	3	1	0.2	5705
Cardiovascular	0.6	0.6	0.7	1	2	0.1	1	2	0	5	9	0.1	2118
Dermatological	115	390	3	97	149	1	36	87	0.7	59	227	2	71974
Genitourinary	0	2	0.2	0	2	1	2	1	0	4	211	0	26349
Hormones	5	0.3	0	7	1	0	14	0.2	0	15	1	0	3588
Anti-infectives	815	112	0.4	1150	17	0.6	344	93	1	329	61	11	170308
Antineoplastic	0.1	0	0	2	0	0	2	0.4	0	4	0.1	0	752
Musculoskeletal	0	0.1	5	0	0	4	0.1	1	2	2	10	24	4836
Nervous system	9	1	0.1	26	2	0.5	50	5	5	58	15	20	17384
Antiparasitic	18	0	0.6	66	0	3	41	0	0.2	23	0	0.2	10056
Respiratory	118	465	24	747	46	4	349	18	0.3	229	3	0.3	115485
Sensory organs	152	97	0.1	117	67	0.1	38	25	0	31	15	0.1	27419
Total	1375	1090	35	2233	299	16	889	251	10	796	575	61	467334

3.1.6.1.1. Anti-infectives

Anti-infectives were by far the most commonly prescribed ATC group. Amoxicillin- clavulanic acid tablets were extensively prescribed for all age groups.

3.1.6.1.2. Dermatological medicinal products

The majority of dermatological medicinal products were prescribed off-label. The most frequent prescribed off-label medicinal products in children below 12 years of age were topical hydrocortisone and clorhexidine combinations. Topical anti-acne drugs aselainic acid and adapalene were the most commonly prescribed off-label drugs for adolescents.

3.1.6.1.3. Respiratory system medicinal products

Over half of the prescriptions for respiratory medicinal products were off-label. Frequently prescribed off-label respiratory medicinal products for infants and toddlers were oral cetirizine drops, followed by salbutamol syrup and mometasone nasal spray.

3.1.6.1.4. Medicinal products for sensory organs

Among the medicinal products for sensory organs, chloramphenicol ophthalmic drops accounted for most of the off-label use.

3.1.6.1.5. Medicinal products for the alimentary tract

The most common off-label prescribed medicinal products for the alimentary tract for infants and toddlers were multienzymes. Drotaverine tablets was the most common used medicinal product in preschool- and school children.

3.1.6.1.6. Genitourinary tract medicinal products

A high off-label use was registered among genitourinary medicinal products prescribed for adolescents. Over 20.000 prescriptions for hormonal contraceptives were issued, which have no information about the use in the paediatric population.

3.1.7. Finland

We estimated the frequency with which medicinal products belonging to various ATC classes appeared in the submitted list. The limitations of this approach were known to us.

Analgesics and psycholeptics, anti-infectives for systemic use, antiarrhythmics, beta-blockers and antacids were mentioned most frequently. 68% of the medicines were used for treatment, 10% for treatment and prophylaxis and 2% for prophylaxis only. For the remaining 20% of the cases, data was not available.

3.1.7.1. Off-label use – overall view

57% of the medicinal products reported in the submitted database were used off-label. Antibacterials for systemic use, psycholeptics, analgesics, antiepileptics and antiinflamatory products were mentioned most frequently as having been prescribed off-label. 62% of the medicines were use for treatment, 9% for treatment and prophylaxis and 3% for prophylaxis only. Missing data accounted for the remaining 26%.

3.1.7.1.1. Off-label use in inpatients

The most frequently reported medicinal products used off-label in inpatients were antivirals for systemic use, solutions for parenteral nutrition, haemostatics, antiepileptics and general anaesthetics. 41% of the medicines were used for treatment, 5% for treatment and prophylaxis and 4% for prophylaxis only (the remaining 49% was not available for the analysis).

3.1.7.1.2. Off-label use in outpatients

Non-steroid antiinflamatory products, followed by antipsychotics and antidepressants, lipid lowering agents and anti-migraine preparations were the most mentioned medicinal products in outpatients. 78% of the medicinal products were used for treatment, 9% for treatment and prophylaxis, 1% for prophylaxis only and another 1% for treatment and diagnosis. Data was not submitted for the remaining 11% of the cases.

3.1.8. France

3.1.8.1. Unauthorised use of medicinal products in children (compassionate use data)

The submitted dataset covered the period between January 2007 and December 2008. Children represented 24% of the total number of patients treated in 2007 with products temporary authorised for use. During 2008, 127 such products were used for the treatment of children.

The corresponding ATC codes (if available) were added before the data analysis, as no quantitative measurement of the extent of use was reported. An estimation of the extent of use was performed by analysing the frequency of appearance of the medicinal products belonging to the various ATC classes on the compassionate use list. Anti-infectives for systemic use, and antiepileptics were among those mentioned most frequently.

3.1.8.2. Off-label use of medicinal products

3.1.8.2.1. Data on extemporaneous preparations

44% and 48% of the extemporaneous preparations used in inpatients were manufactured for an intended use in children during 2007 and respectively 2008. This corresponded to a volume of 1163 different preparations corresponding to 210 different substances (INN) in 2008.

Antiarrhythmics and beta-blockers, solutions for parenteral nutrition, proton pump inhibitors and H2-receptor inhibitors were among the most frequently mentioned.

3.1.8.2.2. Hospital dispensing data

Data covering the period July - December 2008 were submitted. 5106 children were prescribed a total of 60,086 prescriptions, 15,466 of which were prescriptions for off-label medicines (25,7%). The twenty most frequent INNs (ranked in descending order by the number of daily prescriptions issued) used off-label are summarised in the table below:

1. Lansoprazole	11.Phloroglucinol
2. Salbutamol	12.Amoxicillin+clavulanic acid
3. Rifamycin	13.Metopimazine
4. Pantoprazole	14.Infliximab
5. Folic acid	15.Calcium carbonate + vitamin D3
6. Albumin	16.Amphotericin B
7. Nalbuphine	17.Sulfamethoxazole-trimethoprim
8. Enoxaparin	18.Ranitidine
9. Ferrous fumarate	19.Nifedipine
10. Ketoprofen	20.Metoclopramid

The most frequent routes of administration were the oral and intravenous routes. The top 10 substances (ranked in descending order by the number of daily prescriptions issued) used for each of the two routes mentioned above are summarised below:

Oral route	Intravenous route
1. Lansoprazole	1. Pantoprazole
2. Folic acid	2. Albumin
3. Ferrous fumarate	3. Ketoprofen
4. Calcium carbonate and vitamin D3	4. Metopimazine
5. Amphotericin B	5. Phloroglucinol
6. Sulfamethoxazole-trimethoprim	6. Infliximab
7. Nifedipine	7. Ranitidine
8. Ursodeoxycholic acid	8. Amoxicillin+clavulanic acid
9. Enalapril maleate	9. Metoclopramid
10. Prednisolone	10. Ketamine

Because of the data heterogeneity, we did not perform any analysis related to the paediatric age groups.

3.1.8.3. Authorised use of medicinal products in outpatients

165 marketed products with a French marketing authorisation were prescribed in paediatric outpatients in the period June 2007 - May 2008 and 16382 different prescriptions were issued.

The most frequent used medicinal products (ranked in descending order by the number of prescriptions issued) are summarised below:

1.Paracetamol	11.Amoxicillin
2.Tixocortol	12.Vaccine: measles, mumps and rubella
3.Helicidine	13.Fenspiride
4.Ibuprofen	14.Niflumic acid + morniflumate + hexetidine
5.2-thiophenecarboxylic acid	15.Amoxicillin + clavulanic acid
6.Oxomemazine	16.Racecadotril
7.Cefpodoxime	17.Phloroglucinol + trimethoxybenzene
8.Acetylcysteine + tuaminoheptane	18.Colecalciferol + fluorine
9.Vaccine: pneumococcal (including conjugated)	19.Trimebutine
10.Betamethasone	20.Domperidone

3.1.9. Hungary

3.1.9.1. Off-label medicinal products in use

3.1.9.1.1. Name of off-label medicine used

Gastroenterological products (azathioprine, budesonide and mesalazine - for treating paediatric inflammatory bowel disease, glicerin, lactulose and sennoside B - as laxatives), antihypertensives (amlodipine, metoprolol, valsartan, enalapril, prazosin), respiratory tract diseases medicines (budesonide, ciclesonide, fluticasone, montelukast, salmeterol and formoterol - alone and in combinations), antibiotics (ciprofloxacin, clarithromycin and meropenem in neonates, doxycicline and neomycin, imipenem plus cilastatin) and haemato-oncological medicinal products were mentioned on the submitted list. An in-depth analysis was not possible.

3.1.9.1.2. ATC classification of off-label medicines used in outpatients

Calcium channel blockers and agents acting on the renin-angiotensin system, psycholeptics, psychoanaleptics and medicines targeting the acid-related disorders were used most frequent.

3.1.9.2. Authorised medicinal products in use

3.1.9.2.1. Name of authorised medicine used

Risperidone filmed tablets (4%) lamotrigine tablets (2%), amoxicillin filmed tablets and darbopoetin alpha solution for injection (2% each) were the most common used authorised medicinal product in the paediatric population.

3.1.9.2.2. ATC classification

Erythropoietin and erythropoietin-like substances (12%), antipsychotics (mainly risperidone) (10%) and antiepileptics (mainly lamotrigine) (10%) were the most frequent used authorised medicinal products.

3.1.10. Iceland

The first 10 most frequently used medicinal products were identified. It was not possible to distinguish between the different types of uses, as no information on the regulatory status of the medicinal products was provided. Information on the age groups in which the medicinal products were used is also considered below.

3.1.10.1. Medicinal products in use

The most frequent 10 used medicinal products in children in Iceland are listed in the following table:

1.Methylphenidate	6.Fluticasone
2.Drospirenone and estrogen	7.Amoxicillin
3.Salbutamol	8.Hydrocortisone butyrate
4.Levonorgestrel and estrogen	9.Sertraline
5.Salmeterol	10.Amoxicillin and enzyme inhibitor

3.1.10.1.1. Medicinal products used in the age group birth to under 1 year

The most frequently used 10 medicinal products in this age group are listed below:

1.Salbutamol	6.Hydrocortisone butyrate
2.Fluticasone	7.Omeprazole
3.Amoxicillin	8.Nystatin
4.Amoxicillin and enzyme inhibitor	9.Fusidic acid
5.Salmeterol	10.Hydrocortisone

3.1.10.1.2. Medicinal products used in the age group 1 to under 2 years

The most frequently used 10 medicinal products in this age group are listed below:

1.Salbutamol	6.Hydrocortisone butyrate
2.Fluticasone	7.Fusidic acid
3.Salmeterol	8.Hydrocortisone
4.Amoxicillin and enzyme inhibitor	9.Alimemazine
5.Amoxicillin	10.Clobetasone

3.1.10.1.3. Medicinal products used in the age group 2 to under 6 years

The most frequently used 10 medicinal products in this age group are listed below:

1.Salbutamol	6.Hydrocortisone butirate
2.Salmeterol	7.Fusidic acid
3.Flutícasone	8.Methylphenidate
4.Amoxicillin	9.Mometasone
5.Amoxicillin and enzyme inhibitor	10.Hydrocortisone

3.1.10.1.4. Medicinal products used in the age group 6 to under 12 years

The most frequently used 10 medicinal products in this age group are listed below:

1.Methylphenidate	6.Hydrocortisone butyrate
2.Loratadine	7.Fluticasone
3.Amitriptyline	8.Amoxicillin
4.Salmeterol	9.Desmopressine
5.Salbutamol	10.Sertraline

3.1.10.1.5. Medicinal products used in the age group 12 to under 18 years

The most frequently used 10 medicinal products in this age group are listed below:

1.Methylphenidate	6.Doxycycline
2.Drospirenone and ethynylestradiol	7.Gestoden and estrogens
3.Levonorgestrel and estrogens	8.Fluoxetine
4.Sertraline	9.Loratadine
5.Desorgestrel and estrogens	10.Mometasone

3.1.11. Republic of Ireland

A detailed breakdown and analysis of all unauthorised use data collected was carried out using the following criteria: name of unauthorised medicine in use, pharmaceutical form of the medicinal product and the regulatory status of the used medicine. A total of 258 unauthorised medicinal products were identified.

3.1.11.1. Unauthorised medicinal products in use

3.1.11.1.1. Name of unauthorised medicine used

Diclofenac in suppository form was the most common unauthorised medicinal product used to treat 15% of the inpatients. Morphine was used unauthorised to treat 14.5% of the inpatients. Halothane (12.5%) and chloral hydrate (syrup) (7.5%) followed. Other unauthorised medicines used in children included pyridoxine, dexamethasone, mercaptopurine and codeine phosphate.

3.1.11.1.2. Medicinal product pharmaceutical form

The most frequent pharmaceutical forms used unauthorised were solutions for injection(38%), followed by tablets (20%), liquids (12%) and suspensions (6%). The remaining 24% were composed of small percentages of drops, powders, suppositories, solutions, gels, creams, ointments, capsules etc. The above information relates to hospital use.

3.1.11.1.3. Authorisation status of unauthorised paediatric medicinal products in other jurisdictions

The third criterion for data analysis was the comparison of authorisation status of the medicinal products in other jurisdictions. 51% of the unauthorised medicinal products were authorised in the United Kingdom, 6% in Germany, 4% in France and the United States and 2% in Italy and Canada. Of note, 31% of the unauthorised medicinal products identified were not authorised in any jurisdiction.

3.1.11.2. Off-label Medicinal Products

3.1.11.2.1. Off-label in relation to age

15% of the medicinal products in the hospital pharmacies were used off-label in relation to age.

The medicines identified were grouped into categories based on ATC codes; categories with a high percentage of off-label use (>8%) were grouped into therapeutic areas as previously described.

3.1.11.2.1.1. Cardiovascular medicinal products used off-label (age)

Antihypertensives (34%) and antiarrhythmics (16%) are the two therapeutic groups most frequent used off-label in relation to age (24% of the total off-label usage).

3.1.11.2.1.2. Alimentary and metabolism medicinal products used off-label (age)

This therapeutic class was the second largest (13% of the total). H_2-receptor antagonists (18%), proton pump inhibitors (15%) and antacids (14%) were most commonly used off-label in relation to age.

3.1.11.2.1.3. Nervous system medicinal products used off-label (age)

This therapeutic class had the third highest incidence of off-label use in relation to age (12%). Antipsychotics accounted for 23% and opioid analgesics for 22% of off-label use. Three classes of antidepressants were frequently used off-label: selective serotonin uptake inhibitors (15%), tricyclics (12%) and serotonin-norepinephrine reuptake inhibitors (4%).

3.1.11.2.1.4. Dermatological medicinal products used off-label (age)

The off-label use of medicinal products used to treat dermatological conditions represented 10% of the total. Antifungals (34%) and corticosteroids (22%) were on the first two places.

3.1.11.2.1.5. Blood and blood-forming medicinal products used off-label (age)

This therapeutic class accounted for 9% of off-label use in relation to age, with anticoagulants (38%) and iron supplements (22%) being the leading substances.

3.1.11.2.1.6. Sensory organ medicinal products used off-label (age)

This class represents 8% of the total. Ocular lubricants (25%) and anti-inflammatory preparations (19%) were the most common used.

3.1.11.2.2. Centrally Authorised Medicinal Products

77 centralised medicinal products were identified in the hospital pharmacies. 20% of them were used off-label in relation to age.

3.1.12. Lithuania

Information on 328 medicinal products (including different pharmaceutical forms, strengths and pharmaceutical forms) was available. The performed analysis was descriptive and was limited due to the absence of the quantitative measurement of the extent of use.

The absence of information on the regulatory status of the medicinal products listed was a further limitation. A brief description of submitted data for information purposes is presented below.

3.1.12.1. Treatment intention

88% of the medicines were use for treatment, 8% were used for treatment and prophylaxis, 2% for diagnosis and 2% for prevention only.

3.1.12.2. Route of administration

49 % of used medicinal products were administered orally and 34% were the substances for intravenous use.

3.1.12.3. Name of the medicinal product

Diazepam, acetaminophen, acyclovir, methylprednisolone and amoxicillin were mentioned most frequently in the submitted dataset. As already mentioned, it was not possible to distinguish between the different types of uses of the medicinal products.

3.1.13. Latvia

469 different medicinal products were included in the dataset. The most important limitation of the submitted dataset was the cumulative reporting of the authorised and non-authorised uses of medicines.

The results of a brief descriptive analysis are presented below for information purposes.

3.1.13.1. Name of medicinal product used

Paracetamol, human insulins, valproic acid, diclofenac, and methyl prednisolone were mentioned most frequent in the submitted database.

3.1.13.2. Pharmaceutical form of the medicinal products used

Use of vials accounted for 36% of all reported uses of medicinal products; use of tablets accounted for an additional 26%.

3.1.13.3. ATC classification of used medicines

Local anaesthetics, analgesics and antipyretics, anti-infectives for systemic use (mainly macrolides) and antidiabetics for systemic use (various types of insulins) were frequently mentioned.

3.1.14. Malta

Submitted data provided inconstant information on the off-label use of the medicinal products in the paediatric population. No estimation of the extent of use was provided. A brief descriptive analysis of the submitted dataset is provided below.

Information on 732 medicines (including different pharmaceutical forms, strengths and formulations) was submitted. 16% of the medicines were used in inpatients and 46% were used in both in- and outpatients. 15% were prescribed by various specialist doctors and 51% were prescribed by a paediatrician or by a general practitioner.

Antiepileptics, immunosuppressants, bronchodilators and antiemetics were mentioned most frequent.

3.1.15. The Netherlands

A descriptive analysis was performed based only on the pharmacies survey data. The results refer to the use of authorised products in outpatients. The quantitative measurement of the extent of use is the number of prescriptions for each medicinal product.

3.1.15.1. Overall prescriptions of authorised medicinal products for the paediatric outpatients

Amoxicillin (8% of all prescriptions), salbutamol (6%), levonorgestrel and oestrogens (6%), fluticasone (4%) and fusidic acid (3%) were prescribed most frequent. The first 50 most prescribed medicinal products represents approx. 75% of all prescriptions.

3.1.15.2. Prescriptions of authorised medicinal products in relation to age

3.1.15.2.1. Age group from birth to 1 year

Betalactamines (17% of the total number of prescriptions in this age group), inhalative beta-agonists (8%) and the antimicrobials for intestinal use(7%) were the medicinal products most prescribed.

3.1.15.2.2. Age group from 2 to 12 years

Betalactam antibiotics (13%), inhalative beta-adrenergic agonists, glucocorticoids (14 % altogether) and corticosteroids for topical use (6%) were the most prescribed medicines in this age group.

3.1.15.2.3. Age group from 13 to 18 years

Oral contraceptives (14%), antihistamines for systemic use (6%), stomatological preparations (5%) and inhalative beta-adrenergic agonists (5%) were the most prescribed medicines in this age group.

3.1.16. Norway

The analysis was performed used the following criteria:

- for unauthorised medicinal products: in/outpatient status, name of the active substance, pharmaceutical form, age group;

- for authorised medicinal products used off-label: name of the active substance

3.1.16.1. Active substances used unauthorised in outpatients

3.1.16.1.1. Name of the active substance used unauthorised

Melatonin (50%) and pentoxyverine (15%) were the most commonly prescribed active substances used unauthorised in the paediatric population.

3.1.16.1.1.1. Name of the active substances used unauthorised in outpatient children from birth to less than 1 year of age

Phytomenadione (23%), melatonin (18%) and betamethasone (15%) were the most frequent three active substances used unauthorised in this age group.

3.1.16.1.1.2. Name of the active substances used unauthorised in outpatient children from 1 to 2 years of age

Pentoxyverine (42%), betamethasone (15%), melatonin (10%) and epinephrine (7%) were the most frequent active substances used unauthorised in this age group.

3.1.16.1.1.3. Name of the active substances used unauthorised in outpatient children from 3 to 5 years of age

In this age group, pentoxyverine (40%), melatonin (18%), betamethasone (13%) and epinephrine (4%) were the most frequent active substances used unauthorised.

3.1.16.1.1.4. Name of the active substances used unauthorised in outpatient children from 6 to 11 years of age

Melatonin (60%), pentoxyverine (12%) and midazolam (4%) were the most frequent three active substances used unauthorised in this age group.

3.1.16.1.1.5. Name of the active substances used unauthorised in outpatient children from 12 to under 18 years of age

Melatonin (58%) and pentoxyverine (6%) were the most frequent active substances used unauthorised in older children and adolescents.

3.1.16.1.2. Pharmaceutical form of the active substance used unauthorised

The most frequent pharmaceutical forms for the active substances used unauthorised in children were tablets (85%), capsules (1%) and oral solutions (1%).

3.1.16.2. Active substances used unauthorised in inpatients

3.1.16.2.1. Name of active substance used unauthorised

Dexamethasone (14%) and epinephrine (14%) were the most commonly prescribed active substances used unauthorised in inpatient children of all ages.

3.1.16.2.1.1. Name of active substances used unauthorised in inpatient neonates

Folic acid (57%), calcium glubionate (10%) and dexamethasone (8%) were the most frequent three active substances used unauthorised.

3.1.16.2.1.2. Name of active substances used unauthorised in inpatient children from more than 1 month to less than 18 years of age

Epinephrine and dexamethasone (15% each), followed by melatonin and betamethasone (12% each) and baclofen (11%) were most frequent used unauthorised in this age group.

3.1.16.2.2. Pharmaceutical form of the active substances used unauthorised

Tablets (31%), solutions for injection (30%), inhalative medicinal products (14%) and oral solutions (12%) were the most frequent used pharmaceutical forms of the active substances used unauthorised.

3.1.16.3. Active substances used off-label in outpatients

3.1.16.3.1. Name of the active substance used off-label

Oral contraceptives (drospirenone and estrogen, desestrogel and estrogen, norethisterone, norethisterone and estrogen, desorgestrel (together 45%), followed by ketoprofen (4%) were most commonly prescribed off-label in the paediatric population.

3.1.16.3.1.1. Name of medicines used off-label in outpatient children from birth to less than 1 year of age

Fluticasone (46%), alimemazine (11%) and salbutamol (9%) were the most frequent three active substances used off-label in this age group.

3.1.16.3.1.2. Name of medicines used off-label in outpatient children from 1 to 2 years of age

Bromhexine (18%), triamcinolone, salmeterol (11% each) and codeine (7%) were the most frequent active substances used off-label in this age group.

3.1.16.3.1.3. Name of medicines used off-label in outpatient children from 3 to 5 years of age

Diclofenac, opium derivatives and mometasone (12% each), triamcinolone (8%), budesonide (7%) and bromhexine (5%) were the most frequent active substances used off-label in this age group.

3.1.16.3.1.4. Name of medicines used off-label in outpatient children from 6 to 11 years of age

Atomoxetine (11%), triamcinolone (8%) and ketoprofen (7%) were the most frequent three active substances used off-label in this age group.

3.1.16.3.1.5. Name of medicines used off-label in outpatient children from 12 to under 18 years of age

Oral contraceptives (61%) and ketoprofen(6%) were the most frequent active substances used off-label in older children and adolescents.

3.1.17. Portugal

There was no quantitative measure of the extent of use of medicines in the paediatric population in the submitted dataset. An analysis of a surrogate measurement: the frequency of appearance of medicines belonging to various ATC classes in the submitted list was therefore performed.

Corticosteroids for systemic use, antineoplastic agents, antiepileptics, analgesics and antipyretics were mentioned most frequent.

3.1.17.1. Medicinal products used off-label

Antineoplastic agents, H2-receptor antagonists, proton pump inhibitors, corticosteroids for systemic use, anxiolytics, analgesics and antipyretics were mentioned most frequent as having been used off-label.

3.1.17.1.1. Off-label in relation to pharmaceutical form

Solutions for injection (47%), tablets (36%) and oral solutions (6%) were the pharmaceutical forms most frequently used off-label.

3.1.17.1.2. Off-label in relation to the source of information

9 out of the 22 hospitals participating in the survey submitted off-label use data. Most data were submitted by an oncology hospital (which may explain the leading position of the chemotherapeutic agents).

3.1.18. Romania

The paediatric off-label use was analysed using the following criteria: name of medicinal product used off-label, pharmaceutical form of the medicinal product used off-label, treatment length and total number of patients.

3.1.18.1. Medicinal products used off-label

3.1.18.1.1. Name of medicines used off-label

Ranitidine as solution for injection (31%), drotaverine as solution for injection (23%), norfloxacin for oral use (18%) and famotidine for oral use (13%) were most commonly used off-label in the paediatric population.

3.1.18.1.2. Pharmaceutical form of the medicinal product used off-label

Solutions for injections (53%), followed by the oral pharmaceutical forms (aggregate: 45% of the total use) were the most frequently encountered pharmaceutical forms among the medicinal products used off-label.

3.1.18.1.3. Estimate of the extent of the off-label use

An estimate of the extent of the off-label use was computed by multiplying the annual number of treated patients by the average length of treatment provided. Ranitidine, norfloxacin, famotidine, alprazolam and amlodipine were the most frequent medicinal products used off-label.

3.1.19. Slovenia

Submitted data were broken down according to the the following criteria: name of unauthorised medicine in use, pharmaceutical form and the regulatory status of the medicinal product. 260 unauthorised medicinal products were identified, 97 of which had a marketing authorisation in at least one EU Member State.

3.1.19.1. Unauthorised use of medicinal products

3.1.19.1.1. Name of medicine used unauthorised

Vitamin E as powder for oral use, phenobarbital as tablets, omeprazole as capsules and dextriferron as syrup were the most common medicinal products used unauthorised.

3.1.19.1.2. Pharmaceutical form of the medicinal product used unauthorised

Solutions for injection(20%), tablets (16%) and syrups (8%) were the most frequent pharmaceutical forms used unauthorised. This information relates to inpatients.

3.1.19.1.3. Authorisation status of the medicinal products used unauthorised in the paediatric population in other jurisdictions

37% of the identified medicinal products used unauthorised in the paediatric population were authorised in other jurisdictions within the EU. Additional data on each jurisdiction was not available.

3.1.19.2. Off-label use of medicinal products

3.1.19.2.1. Off-label use in relation to age

The most frequent 10 substances used off-label in all age groups are summarised in the table below:

1. Salbutamol	6.Ranitidine
2. Omeprazol	7. Gentamicin
3. Dextriferron	8. Vitamin C + calcium carbonate + calcium lactate gluconate
4. Metamizol	9. Pantoprazol
5. Aminophylline	10.Miconazole

3.1.19.2.1.1. Off-label use in premature newborns

In this age group, the list of the most frequent 10 medicines used off-label was:

1. Dextriferron	6.Iron succinyl-protein complex
2. Aminophylline	7.Fluconazol
3. Vitamin C+calcium carbonate+calcium lactate gluconate	8.Gentamicin
4. Miconazole	9.Clotrimazole
5. Lyophillised lactic acid bacteria	10.Imipenem+cilastatin

3.1.19.2.1.2. Off-label use in term neonates

Term neonates were treated off-label with the following 10 most used substances:

1. Gentamicin	6.Cefotaxim
2. Tobramycin	7.Lyophillised lactic acid bacteria
3. Metamizol	8.Dopamine

4. Ceftriaxone	9.Midazolam
5. Fentanyl	10.Pantoprazol

3.1.19.2.1.3. Off-label use in infants and toddlers

In this age group, the most frequent medicines used off-label were:

1. Salbutamol	6.Gentamicin
2. Fenoterol + ipratropium bromide	7.Diclofenac
3. Metamizol	8.Methylprednisolone
4. Trimetoprim+sulphamethoxazole	9.Midazolam
5. Furosemid	10.Oxymetazoline

3.1.19.2.1.4. Off-label use in children (aged 2 to 11 years)

The most frequent 10 medicines used off-label in this age group are summarised below:

1. Ranitidine	6.Loratadine
2. Amoxicillin + clavulanic acid	7.Metamizol
3. Salbutamol	8.Omeprazol
4. Acyclovir	9.Pantoprazol
5. Ceftriaxone	10.Acetylsalicilic acid

3.1.19.2.1.5. Off-label use in adolescents

The most frequent 10 medicinal products used off-label in adolescents were:

1. Omeprazol	6.Fluticasone
2. Calcium carbonate	7.Clemastine
3. Calcitriol	8.Olanzapin
4. Warfarin	9.Acetylsalicilic acid
5. Enalapril	10.Ranitidine

3.1.20. Sweden

3.1.20.1. Over-the-counter (OTC) medicines use

Certain medicinal products are sold OTC in children. Questionnaire response analysis showed that children had used 0.9 OTC substances on average. 65% of the children visiting an emergency ward and 67% of the 13 year old Stockholm inhabitants had used at least one OTC medicine.

3.1.20.1.1. Approximation of the total OTC medicine use among Swedish Children

The Summaries of Product Characteristics (SmPC) of medicinal products sold OTC in Sweden in 2007 were analysed to define the age limits for OTC use. An approximation of the percentage of medicine use in the paediatric population was made in view of the following criteria:

Percentage	Interpretation
0	Not likely to be used OTC in children (e.g. topical minoxidil)
1	Could be used by children as OTC and to some extent among adolescents (e.g. omeprazole, nicotine).
10	Use of OTC to some extent in a specific age group such as adolescents or children (e.g. naproxen, ketoprofen)
20	Use of OTC in the same extent as in the adult population (e.g. loratadin tablets, paracetamol tablets)
99	Almost exclusively used by children OTC (e.g. paracetamol oral liquid, xylometazolin lower strength)

A factor was developed to estimate the number of packages used OTC in children.

The total number of packages sold for each medicine was multiplied with the factor described above and grouped with regard to the ATC classification and the pharmaceutical form. The total number of Swedish children in 2007 was collected from the Swedish Statistical Bureau(SCB).

3.1.20.1.1.1. Number and name of medicinal products sold as OTC

10.4 million packages were sold OTC for the paediatric use (5 OTC medicine packages/child x year). Paracetamol (30%), oxymetazoline (11%), xylometazoline (7%), ibuprofen (7%) and bromhexine (6%) were the most frequent sold substances. 11% of the packages sold lacked information on paediatric dosage. Caffeine and levonorgestrel were the most frequent tablets sold OTC.

3.1.20.1.1.2. Pharmaceutical forms of medicinal products sold as OTC

The pharmaceutical forms estimated to be sold OTC for children were: tablets (28%), oral liquids (18%), nose applications (18%), topical formulations (12%) and rectal formulations (8%).

3.1.20.1.2. Analysis of the off-label use of OTC medicines among a selected population of Swedish children living in Stockholm

The proposed questionnaire was answered by 2823 children (1416 boys/1407 girls) with a mean weight of 48±9.8 kg and a mean age of 13±0.8 years. 1885 patients (67%) reported use of one or more of the 2550 OTC medicines (0.9 OTC medicines / person). All participating children were over 12 years old and all substances used were on-label with regard to age limits presented in the registered package insert.

The most frequently used OTC medicines were paracetamol (48.2%), ibuprofen (14.5%), antihistamines for systemic use (11.3%) and anti-allergic products for intraocular use (7.2%).

3.1.20.1.3. OTC medicine use in paediatric outpatients (children visiting an emergency department)

274 out of the 960 paediatric patients visiting the emergency department (28,5%) answered the questionnaire (mean age= 3.99 years). More than 50% were aged from birth to 2 years of age with a small overrepresentation of boys (52%).

Each patient/parent reported an average total use of 1.7 medicines, of which 0.9 were OTC.

The most frequent used OTC medicines were paracetamol (60%), nasal decongestants(15%), ibuprofen(10%), vitamins (9%) and cough syrup (3%).

3.1.20.2. Paediatric medicine use at hospitals

Data was collected on 1515 paediatric inpatients during a 2-day period rendering in a total of 5566 prescriptions. The average age of the study population was 5.7 years (SD 5.9) (M/F=1,12/1). The most common age-group was children (42%), followed by adolescents (23%), neonates (21%) and infants (14%).

Of all prescribed medicines, 83 % were authorised, 12 % were pharmacy prepared and 4 % unlicensed medicines. The highest proportion of unauthorised medicinal products was found among ATC class A, for example liquid multivitamins. Medicines for the nervous system, (for example i.v. morphine and oral and intravenous caffeine citrate) constituted the highest proportion of extemporaneously prepared medicines.

40% of all prescriptions were products for intravenous use and 42% were oral forms. 50% of the prescriptions were used for treatment, 34% for prevention and 7% for both. The most common treatment indication was pain (N=739), followed by conditions associated with prematurity (N=349), infection (N=186), heart failure (N=107) and nutrition difficulties (N=106).

3.1.20.2.1. Authorised medicinal products

The group of medicinal products most commonly prescribed, classified according to the ATC codes, was ATC-N, followed by ATC-B. The most common medicinal products prescribed were paracetamol (12%), followed by intravenous carbohydrates (6%) and electrolyte solutions (3%).

3.1.20.2.2. Medicinal products used off-label

The proportion of *off-label* medicinal use was 35% of all prescriptions of authorised medical products. The highest use of off-label drug use was found among drugs for the nervous system, e.g. morphine, as well as medicines for blood or blood forming organs, e.g. intravenous glucose.

The highest proportion, although low in numbers, was found among topical dermatological (ATC group D) and the ophthalmologic (ATC group S) medicines.

More than 200 prescribed medicinal products were administered off-label, most commonly intravenous formulations that were administered orally.

Infants represented the most common age group receiving at least one medicinal product *off-label;* they were followed by neonates and children (table 1). Use of at least one extemporaneously prepared medicinal product, as well as use of unauthorised medicinal products, was most frequent in the neonatal age group.

Table 1: Percentage of patients with **at least one** prescription of licensed, off-label, pharmacy prepared or unauthorized medicinal product, respectively, by age group.

Age groups	All Patients (N)	Prescription /Patient (N)	Licensed (%)	*Off-label* (%)	Pharmacy prepared (%)	Unauthorized (%)
Neonates	313	4.0	82	57	45	32

Age groups	All Patients (N)	Prescription /Patient (N)	Licensed (%)	*Off-label* (%)	Pharmacy prepared (%)	Unauthorized (%)
Infants	205	4.1	95	67	27	19
Children	641	3.4	96	57	23	4
Adolescents	355	3.7	98	37	19	7

3.1.20.3. Off-label use in paediatric outpatients

We analyzed the number of prescriptions dispensed for each medicinal product, grouped by ATC class and age (proposed age distribution: 0-27 days, 28 days- less than 6 months, 6 months- less than 1 year, 2years – less than 6 years, 6 years – less than 12 years, 12 years – less than 16 years and 16 years – less than 18 years).

898 different medicinal products (2.2 million prescriptions) were dispensed to paediatric patients in Sweden and 393 substances were dispensed more than 100 times. Age limits for the authorised use in paediatrics were identified for 386 substances.

36% of the 386 substances were classified as having had an authorised use whereas 64% had at least once been used as off-label with respect to the patient's age at the time of prescribing.

The 247 substances used off-label were dispensed 1.02 million times (around 290 000 were off-label with respect to age).

13.5% of the prescriptions were off-label with regard to age of the patient.

3.1.20.3.1. Off-label use by ATC class

ATC classes J and R were dispensed most commonly, but had both a low off-label prescription rate (0,1% and 3,1% respectively). In contrast, ATC group G had a very high off-label prescription rate (97,3%), despite it being less often dispensed.

3.1.20.3.2. Off-label use by age group

The tables below show the most frequently used medicinal products by age group:

Top 10 substances used off-label (all age groups)	
1. Budesonid	6. Diclofenac
2. Opium derivatives and expectorants	7. Formoterol and other anti-asthmatics
3. Cetirizin	8. Fusidic acid
4. Desloratadin	9. Cough suppressors and expectorants
5. Desorgestrel	10. Ibuprofen

Top 10 substances used off-label (age group from birth to 28 days)	
1. Fusidic acid	6. Dicycloverine
2. Chloramphenicol	7. Ceftibuten
3. Trimetoprim	8. Sulphametoxazole plus trimetoprim
4. Nystatin	9. Ferrous fumarate
5. Myconazole and combinations	10. Oxymetazolin

Top 10 substances used off-label (age group from 1 to 6 months)	
1. Fusidic acid	6. Clemastine
2. Absorbed pneumococcal conjugated vaccine	7. Dicycloverine
3. Chloramphenicol	8. Trimetoprim
4. Budesonid	9. Sulphametoxazole plus trimetoprim
5. Myconazole and combinations	10. Ephedrine

Top 10 substances used off-label (age group from 6 to 12 months)	
1. Budesonid	6. Absorbed pneumococcal conjugated vaccine
2. Fusidic acid	7. Myconazole and combinations
3. Chloramphenicol	8. Trimetoprim
4. Clemastine	9. Ibuprofen
5. Sulphametoxazole plus trimetoprim	10. Ceftibuten

Top 10 substances used off-label (age group from 1 to 2 years)	
1. Fusidic acid	6. Cough suppressors and expectorants
2. Clemastine	7. Myconazole and combinations
3. Budesonid	8. Ibuprofen
4. Chloramphenicol	9. Desloratadine
5. Sulphametoxazole plus trimetoprim	10. Absorbed pneumococcal conjugated vaccine

Top 10 substances used off-label (age group from 2 to 5 years)	
1. Clemastine	6. Opium derivatives and expectorants
2. Budesonid	7. Desloratadine
3. Fusidic acid	8. Loratadine
4. Chloramphenicol	9. Sulphametoxazole plus trimetoprim
5. Cough suppressors and expectorants	10. Trimetoprim

Top 10 substances used off-label (age group from 6 to 11 years)	
1. Budesonid	6. Mometasone
2. Clemastine	7. Opium derivatives and expectorants
3. Loratadine	8. Chloramphenicol
4. Desloratadine	9. Cetirizin
5. Fusidic acid	10. Formoterol and other anti-asthmatics

Top 10 substances used off-label (age group from 12 to 15 years)	
1. Levonorgestrel+estrogens	6. Diclofenac
2. Budesonid	7. Loratadine
3. Mometasone	8. Cetirizin
4. Desloratadine	9. Natrium fluoride
5. Opium derivatives and expectorants	10. Formoterol and other anti-asthmatics

Top 10 substances used off-label (age group from 16 to 18 years)	
1. Levonorgestrel+estrogens	6. Pivmecilinam
2. Desorgestrel	7.Opium derivatives and expectorants
3. Diclofenac	8. Norgestimat + estrogens
4. Mometasone	9. Natrium fluoride
5. Budesonid	10. Desloratadine

3.1.20.3.3. Off-label use by route of administration

The most frequent routes of administration used off-label were the oral route, followed by the topical eye application and the inhalative route.

3.1.21. United Kingdom

The United Kingdom referred to the British National Formulary for Children (BNFC) for a data synopsis on the off-label and unauthorised use of medicinal products in the paediatric population. No dataset was submitted.

In section "How BNF for children is constructed" of the above mentioned source it is stated that "BNFC uses about 80 clinical advisers throughout the UK to help with the production of each edition." "These clinical experts help to ensure that BNFC remains reliable by: […] advising on the use of unlicensed medicines or of licensed medicines for unlicensed uses ('off-label' use)".

The information provided by the above-mentioned source on off-label use is put together via an "expert opinion" process. It was not further analysed.

3.2. Data analysis by type of outcome measurement

All attempts of merging the submitted datasets for the purpose of a global analysis were unsuccessful, due to the extreme data heterogeneity.

3.2.1. Defined daily dose as measure of the extent of use

This way of reporting the extent of use was mainly chosen by many countries situated in Northern Europe (Norway, Denmark, Iceland). Of note, some Northern countries (Denmark, Iceland) reported the overall use, while others reported on the off-label use of the medicinal products or on the unauthorised use (Norway).

3.2.2. Other measures of the extent of use

Other measures of quantifying medicines utilisation were used by the Member States in their data sets: number of packages, number of prescriptions, number of patients, cost data. The use of these parameters, although useful for analysing the data set separately and making national comparisons, did not allow for further grouping of the datasets for the purpose of a global analysis and did not enable cross-national comparisons.

4. Summary of main findings

The majority of the submitted data focused on the existing off-label use in children; the few datasets referring to the existing authorised use of medicines are therefore difficult to extrapolate.

The most frequent medicines used off-label and unauthorised belong to the following therapeutic classes: antiarrhythmics, antihypertensives (rennin-angiotensin inhibitors and beta-blockers), proton pump inhibitors and H_2-receptor antagonists, antiasthmatics, and antidepressants (mainly selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants). A high rate of off-label use of oral contraceptives was encountered in adolescents, mainly reported in Scandinavia. There is extensive off-label use of antimicrobials (macrolides, betalactamines plus betalactamase inhibitors and carbapenems) in very young children. Corticosteroids (dexamethasone) are frequently reported to be used off-label in the systemic treatment of very young children. Some steroids for systemic use (e.g. dexamethasone) are not even authorised in some countries (Norway). Most other steroids used off-label in children were topical medicines for dermatologic use.

The analysis of the pharmaceutical forms shows that both oral and parenteral formulations are being used unauthorised or off-label, pointing out at a common reason which is the lack of appropriate dosages and strengths for the treated age groups.

Some of the analysis results are surprising. Among them we mention the off-label use of multivitamins and of many antiasthmatics, despite the high paediatric incidence of this condition.

5. Limitations of the analysis

The analysis above is subject to a number of limitations, some of which are listed below:

1. Data heterogeneity was expected, as the exercise was based on existing data as opposed to performing a prospective survey across the EU. Such a prospective survey would have required extensive resources, including funding. Data heterogeneity therefore reflects different data sets and formats, as available to the different National Competent Authorities. Any international comparison was therefore impossible, as these differences are mostly reflecting methodological differences rather than differences in use.
2. Most datasets could only be considered representative for the specific paediatric subsets in the different individual countries. Different age subsets (when available) had an unbalanced representation in the datasets. For reports on the OTC medicine use it should also be emphasised that it is subject to recall bias.
3. Some Member States did not submit any data; submitted data may not be fully representative, as more than 50% of EU the paediatric population was not covered. Furthermore, the compliance of data submitted with the guidance issued by the Paediatric Committee was actually poor, adding to the complexity of the analysis.
4. Some datasets did not distinguish between authorised, unauthorised and off-label use of medicines. The definitions of the 'uses' of medicinal products (authorised, unauthorised, off-label) were subject to different interpretations (e.g. extemporaneous medicinal products are either considered unauthorised or off-label) in the Member States. In addition, the status of a medicinal product does differ between countries, i.e. a product that is authorised in one Member State is not authorised in another.

5. The absence of an adequate quantitative measurement of the extent of use for some of the datasets analysed led to the analysis of the "number of appearances" of a product or product class in each dataset, which is of very limited value.

6. For datasets using the daily defined dose (DDD) as the quantitative measure of the extent of use: the DDD is defined in adults, so this may be inaccurate in children. Furthermore not all medicines have a WHO-assigned DDD.

7. Every method used to quantify the paediatric extent of use is subject to individual limitations e.g. the number of prescriptions is valuable to evaluate the clinical use of the medicinal product-dosages used per diagnosis, but does not accurately reflect the total use (e.g. if there are several indications per medicinal product).

8. Although off-label and unauthorised use of medicines in children can be seen as a surrogate of the unmet therapeutic needs, the choice of a particular medicines may not be supported by scientific evidence in the majority of cases. It may therefore be more important to focus on the indications treated rather than the active substances themselves.

9. Paediatric safety, which was one of the objectives of the survey, has not been addressed by the data received (only 2 datasets contained some safety data). This reflects the methodological difficulties related to a satisfactory safety reporting.

6. Discussion

Prescriptions of off-label and unauthorised medicines for children is widespread throughout the European Union (between 45-60% of the total number of prescriptions from this survey, confirming the results from previous publications). Both hospitalised children and out-patients are frequently treated with medicines used outside the terms of their marketing authorisation. Higher rates were reported in the premature (up to 90% of prescribed medication) and term neonates and in infants, as well as in patients having serious conditions and being admitted in the intensive care units (both neonates and paediatric). Medicines are mainly used "unapproved" for the treatment of children, with lower figures for prophylactic uses. Not surprisingly, there are differences with regard to the unapproved medicines use across the EU, partially explained by different prescribing habits, but also by the regulatory status (approved or not, in all or some subsets) of the medicinal product in different countries. The main areas of needs include oral contraceptives, which up to now were not studied and approved in adolescents despite identifying potential safety issues with first time users some years ago. This is now addressed by Paediatric investigation Plans. The other main areas are gastro-enterology (reflux), cardiovascular (hypertension), respiratory (asthma). There is a need for clinical trials and supporting evidence for safety and efficacy of anti-asthmatics in children, especially since long term safety concerns were recently reported for the long-acting beta agonists (LABA). This is all the more important as asthma affects principally children. The use of anti-infectives requires supportive evidence in the younger age groups. Although scarce, the data submitted confirm that the neonates, in particular preterm neonates, have high unmet needs. The future will have to address those needs through dedicated trials despite the feasibility issues.

Apart from the situations where the data are missing, from the regulatory point of view, medicines corresponding to the paediatric needs identified may fall under one of the following cases:

a) The medicinal product is authorised in some, but not all the Member States and is therefore used as unauthorised in some countries. A rather simple solution would require regulatory action at Member States level, in particular through the CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures) to make those products available in all the Member

States, for example using MRP or DCP, or making use of the provisions of art. 126a of Directive 2001/83/EC.

b) The medicinal product is authorised, but used off-label in the respective age groups/indication/route of administration/dose/formulation. The follow up of art 45 may lead to widening indications, doses and information if the data submitted are of sufficient quality. Otherwise, it is hoped that the PUMA may answer some of the needs.

c) There is a general lack of paediatric labelling in the SmPC as well as a lack of harmonisation of information between different generic medicines, different routes of administration of the same generic medicine or different pharmaceutical forms of the same medicine. The SmPC does not state the data used by the regulatory authority to authorise the different indications of the product. Regulatory action is needed to foster harmonisation of the paediatric labelling. Applying the revised guideline on SmPC would already take care of some of the discrepancies but will not address the issue of products already authorised for which the SmPC is not going to be revised.

d) The information on existing marketing authorisations at the level of the national competent authorities is difficult to access. Eudrapharm would address this need but in the mean time giving easy access to electronic national databases would help identifying which products are authorised, at which dose and where. This would provide appropriate information to prescribers if the product has been developed and assessed in another Member state.

7. Conclusions

The present report provides an overview of the unmet treatment needs in the paediatric population by analysing the extent of unauthorised and off-label use of medicines in children in the various EU/EEA Member States. The review is not exhaustive and analysed very heterogeneous data. However, it is clear there are wide unmet needs everywhere in Europe. The usefulness of this exercise will mainly be in defining which waiver can or can not be granted by the PDCO. The Committee will still be depending on the submission of applications. The outcome does not provide sufficient information as to the safety (only Austria has submitted some safety data) and generalisability of this data is not certain. However many publications have established that adverse effects are more frequent, more serious and more underreported when medicines are used unauthorised or off-label. It is expected that the Paediatric Regulation will improve the situation by ensuring that new products are meeting paediatric needs through the PIPs agreed by the Paediatric Committee. In the mean time, a number of easy to reach solutions could be proposed at least to make existing medicines available to all Member states and existing information to all prescribers for the sake of European children.

This survey sheds further light on the unacceptable situation of the treatment of children in Europe, which will be addressed by the Paediatric Regulation.